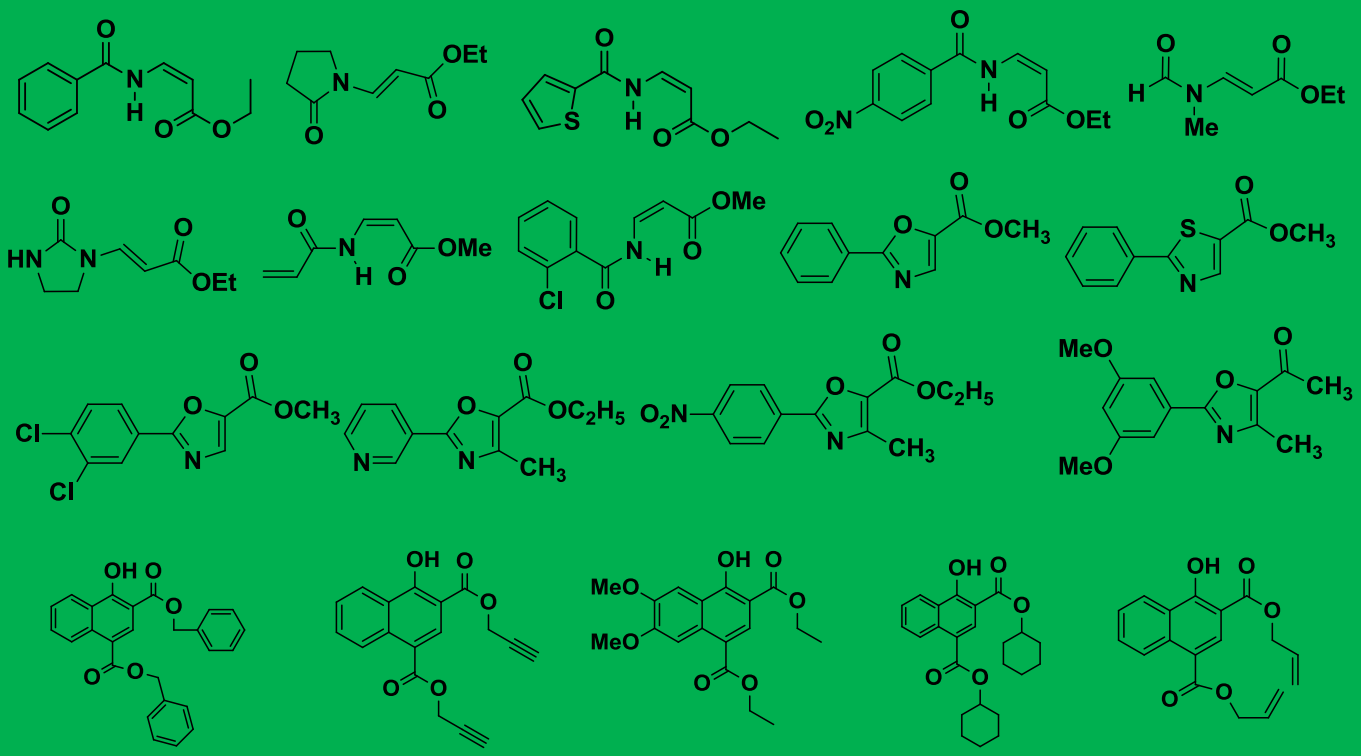
Generation of Enamides and Enol esters: Application to Oxazole and α-Naphthol Synthesis

Raghavender Mothkuri



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Generation of Enamides and Enol esters: Application to Oxazole and α-Naphthol Synthesis

Thesis submitted to

National Institute of Technology Rourkela

for the degree of

Doctor of Philosophy

By

Raghavender Mothkuri

Under the guidance of

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… Dedicated to my family

"I never did anything by accident, nor did any of my inventions come by accident; they came by work"

Thomas Alva Edison
(1847-1931)

NATIONAL INSTITUTE OF TECHNOLOGY
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Certificate

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This is to certify that the thesis entitled "***Generation of Enamides and Enol esters: Application to Oxazole and α-Naphthol Synthesis***" being submitted by Raghavender Mothkuri, to the National Institute of Technology Rourkela, India, for the award of the degree of ***Doctor of Philosophy*** is a record of bonafide research carried out by him under my supervision. I am satisfied that the thesis has reached the standard fulfilling the requirements of the regulations relating to the nature of the degree. The contents of the thesis have not been submitted to any other university or institute for the award of any other degree or diploma.

Date: **Dr. Niranjan Panda**

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Date:

NIT Rourkela **Raghavender Mothkuri**

Biography

Mr. Raghavender Mothkuri was born at Gottimukla (Vikarabad), Rangareddy, Telangana on 7th Nov, 1982. He has received Bachelor of Science with honours in chemistry from Sri Anatnha Padmanabha College, Vikarabad, Osmania University in 2003. He successfully completed the M.Sc. programme in 2006 from the Kakatiya university campus. He also worked as a research chemist for Natco Research Center, Hyderabad. He joined at the Department of Chemistry, National Institute of Technology Rourkela, as a research scholar. During his doctoral programme, he has published the scientific work in many reputed international journals, which mainly include ***Journal of Organic Chemistry, ACS Catalysis, Advanced Synthesis & Catalysis, European Journal of Organic Chemistry, New Journal of Chem*istry**. He also attended various national and international symposium, conference etc. His area of interest includes synthetic methodology and bioactive natural product synthesis, organometallic chemistry and heterocyclic chemistry. The interests are not confined and can be acclimatized to related research areas.

ABSTRACT

Enamides are key structural motifs in many natural products as well as pharmaceutically important metabolites. Furthermore, these are also synthons in numerous organic transformations. For instance, enamides undergo pericyclic reactions, photochemical reactions, nucleophilic reactions to produce chiral amines, electrophilic reaction to produce chiral amides, transition metal catalyzed reactions etc. Enamides are also used extensively for the synthesis of various heterocyclic compounds. Considering the numerous applications of enamides, several methods have been developed for their synthesis. Moreover, controls of stereochemistry across the double bond of enamide persuade a potential problem, particularly in the synthesis of thermodynamically disfavoured *Z*-enamides. Thus, it is highly desirable to develop general and practical methods for the stereoselective preparation of thermodynamically disfavourable *Z*-enamides under mild reaction conditions.

The oxygen analogue of enamide called "*enol ester*" is also an important building block in organic synthesis. Like enamides, enol ester motif is also abundant in numerous natural products as well as pharmaceuticals. Therefore, synthesis as well as the use of enol esters in organic transformation is an attractive area of research in recent years.

Our effort on the synthesis of enamides (particularly *Z*-enamide) and enol esters and their application is presented in this thesis.

The present thesis entitled "***Generation of Enamides and Enol Esters: Their Application in Oxazole and α-Naphthol Synthesis***" has been divided into two parts: *Part-I* and *Part -II*. Part-I divided into four Chapters whereas Part-II divided into two chapters. Brief summary of the chapters are as follows:

Part-I

Chapter 1. Synthesis and Reactions of Enamides: A Brief Overview

In this chapter up to date developments in the use of enamides in various transformations and their synthesis is described. Scope and limitations of the earlier works along with the objective of the present work have been presented briefly.

Chapter 2. Stereoselective Synthesis of Enamides by Palladium-catalyzed Oxidative Amidation of Alkenes

This chapter describes the development of a novel catalytic protocol for the synthesis of Z-enamides by the oxidative amidation of olefins in the presence of ambient air.This protocol is also found to be suitable for the cross coupling of sterically hindered secondary amides with electron deficient olefins leading to tertiary enamides in good yield.

Chapter 3. Stereoselective Synthesis of Enamides by Pd-Catalyzed Hydroamidation of Electron Deficient Terminal Alkynes

This chapter reveals the first Pd-catalyzed hydroamidation of activated terminal alkynes to form *Z*-enamides selectively.The optimized cross-coupling reaction condition is found to be tolerant for the coupling of wide varieties of amides with electron deficient alkynes. A plausible catalytic cycle for the hydroamidation reaction also described.

Chapter 4. Synthesis of substituted oxazoles from enamides

In this chapter, NBS/Me_2S-mediated annulation of enamides into 2,5- and 2,4,5-substituted oxazoles in the presence of mild base has been described. The developed reaction conditions are simple and tolerant to a wide variety of substituents including both electron-donating and withdrawing groups to produce oxazoles in one-pot without further purification of the intermediate.

Part - II

Chapter 5.Enol Esters in Organic Synthesis: A Brief Overview

A brief review on the generation and reactions of enol esters was presented in this chapter. Moreover, objective of the present work in line with the enol-ester chemistry is also mentioned.

Chapter 6. Synthesis of α-naphthols from Enol Esters

In this chapter, development of a *de novo* method for the synthesis of polysubstituted α-naphthols from simple monocyclic enol esters has been demonstrated. The developed reaction conditions are mild and do not require any anhydrous medium or expensive catalytic protocol to access α-naphthols in good yield.

Abbreviations

Acetonitrile	CH_3CN
Acetyl acetone	acac
Ammonia	NH_3
1,1'-Bi-2-naphthol	BINOL
bis(oxazoline)	BOX
4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene	Xantphos
Cesium Carbonate	Cs_2CO_3
Copper acetate	$Cu(OAc)_2$
Copper Iodide	CuI
Copper oxide	CuO
Copper triflate	$Cu(OTf)_2$
Copper(I) thiophene-2-carboxylate	CuTC
Cuprous chloride	CuCl
Cupric chloride	$CuCl_2$
Deuterated chloroform	$CDCl_3$
1,4-diazabicyclo[2.2.2]octane	DABCO
1 8-diazabicyclo 5.4.0 undec-7-ene	DBU
Dichloromethane	DCM
Diethylether	Et_2O
N,N´-Dimethylethylenediamine	DMEDA
Dimethoxyethane	DME
Dimethyl Sulfoxide.	DMSO
N,N-Dimethylformamide	DMF
Ethyl acetoactate	EAA
Infrared	IR
Isopropanol	$^{i}PrOH$
Lithium aluminium hydride	$LiAlH_4$

Melting point	mp
N-methylpyrrolidone	NMP
Palladium acetate	$Pd(OAc)_2$
1,10-Phenanthroline	1,10-Phen.
Potasium bromide	KBr
Potasium Carbonate	K_2CO_3
Potasium hydroxide	KOH
Potasium iodide	KI
Potasium phosphate	K_3PO_4
Potasium tertiarybutoxide	^tBuOK
Room temperature	rt
Sodium	Na
Sodium bicarbonate	$NaHCO_3$
Sodium carbonate	Na_2CO_3
Sodium Chloride	NaCl
Sodium sulfate	Na_2SO_4
Tetrabutylammonium bromide	TBAB
Tetrahydrofuran	THF
Tert-Butyl alcohol	^tBuOH
Transition-Metal	TM
Triethylamine	Et_3N (TEA)
Triphenylphosphine	PPh_3
N,N,N´,N´-Tetramethyl Ethylene Diamine	TMEDA
Ultraviolet	UV
Water	H_2O

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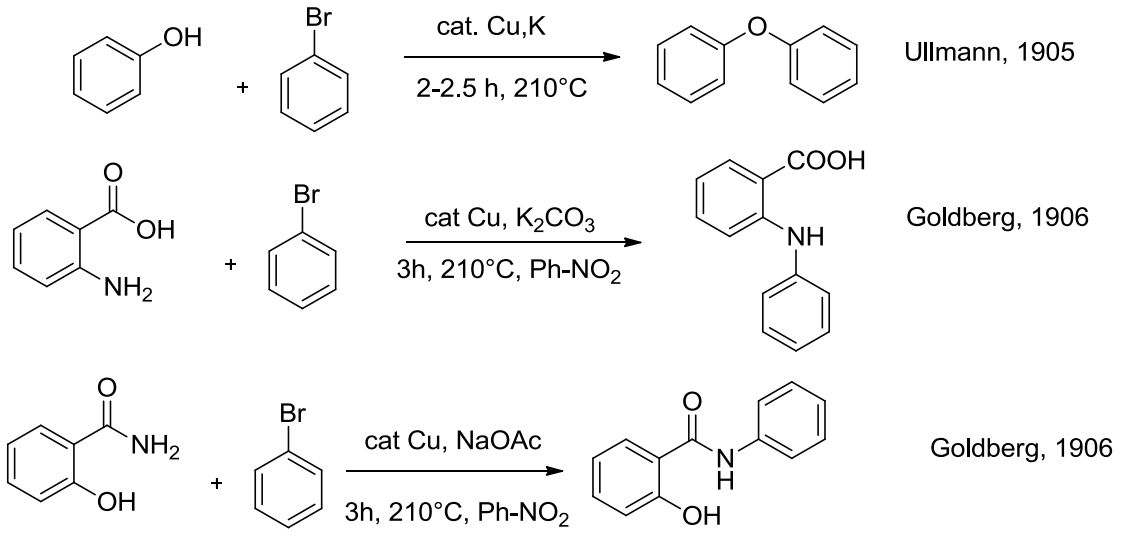
Part - I

Chapter 1

Synthesis and Reactions of Enamides: A Brief Overview

Considering the wide abundance of nitrogenous compounds in nature as well as in pharmaceutical metabolites; carbon-nitrogen (C-N) bond construction has emerged as a pivotal reaction in organic synthesis.[1] In recent years, transition-metal (TM) catalyzed reactions have received paramount attention[2] because of their manifold application in various types of carbon-carbon and carbon-heteroatom bond forming reactions.[3] Indeed, the transition metal mediated C-N bond formation was first reported by Ullmann[4] and Goldberg[5] more than a hundred years ago (Scheme 1).[1a] The classical Ullmann reaction normally requires stoichiometric amounts of Cu-catalyst though catalytic version was reported by Goldberg. Additionally, these protocols require harsh reaction conditions, in particular high temperature (above 200°C). Gratifyingly, numerous efforts have been made by several chemists towards the development of a milder reaction conditions for the C-N bond formation reactions using different transition metal catalysts. Additionally, chemists have also broadened the scope of C-N bond formation reaction towards numerous organic motifs for various applications. In this regard, our attempt towards the Pd-catalyzed C-N bond formation leading to enamides is described in subsequent chapters. A brief review on the generation of enamides and their synthetic application focusing on heterocyclic synthesis is presented here and under.

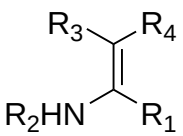
Scheme 1



1.1.1 Enamide: A key structural motif

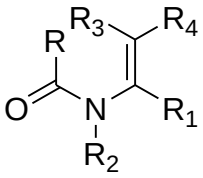
The term "enamine" (e.g. **1**) was coined in 1927 to emphasize the structural similaritiy between the α, β-unsaturated amine system and the α, β-unsaturated alcohol

moiety present in the enols. About 3 decades later, Stork and his associate[6] demonstrated ease preparation of a number of enamines from aldehydes and ketones. They also described the nucleophilic properties of enamines in α-alkylation and α-acylation reactions. This reaction proceeds through the imine or iminium species, which may be subsequently converted to the corresponding carbonyl compounds. The electron donating ability of the nitrogen lone pair to C = C double bond increases the electron density and is responsible for the high nucleophilicity of the enamine.[7a] Usually, the enamines are under equilibrium with its corresponding imine at room temperature. However, when the lone pair of nitrogen is conjugated to a carbonyl group (for example e.g. **2**), the electron density of the C=C decreases and hence the nucleophilic ability of the C=C diminishes. As a result, the stability of the species increases to the extent that, it can be isolated by simple column chromatography. Such species, called enamides[7b] and encarbamates are extremely useful synthetic intermediates in organic transformation particularly in amino acid synthesis[8], heterocyclic synthesis.



1

Enamine



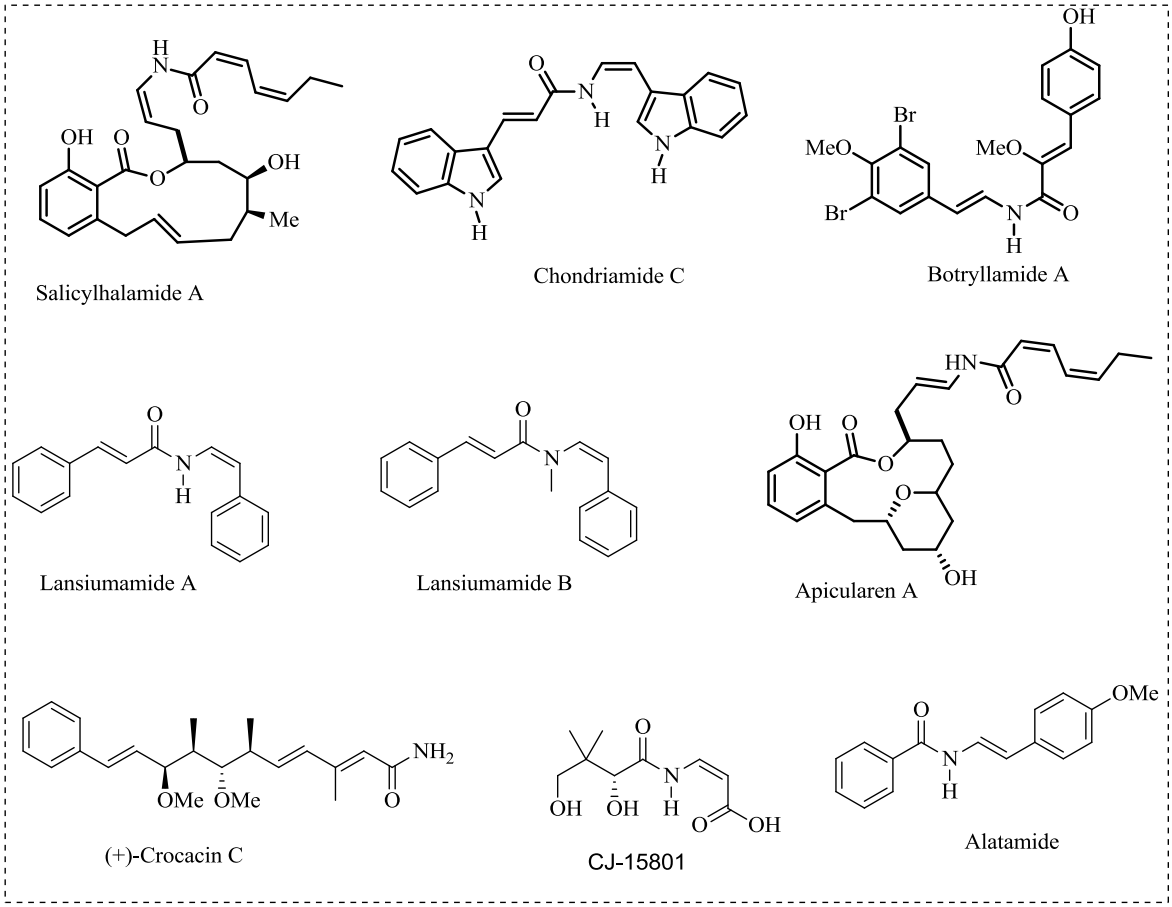
2

Enamide

Enamide motif is omnipresent in numerous natural products such as lansiumamides A-B,[9] lansamide I, crocacins,[10] alatamide,[11] aspergillamides A-B,[12] chondriamide A, C,[13] cyclopeptide alkaloids (e.g., paliurine F_1), and a range of marine metabolites(Figure 1).[14] Furthermore, enamides are also often present in various antibiotics including CJ-15801,[15] pacidamycin D_2[16] etc. These are also common in a number of anti-parasitic and anti-cancer natural products and pharmaceutical drug leads (Figure 1). It is often observed that the enamides unit (–CONH-C=C-) is responsible for the biological activity of some of the compounds through direct involvement in their mode of action.[17] Mechanistically, it has been postulated that protonation of the enamide moiety leads to the highly electrophilic *N*-acyliminium ion that, in turn, can undergo enzymatic nucleophilic attack to form the conjugated adduct; responsible for the activity. Enamides are also used as monomers in polymerization reactions. For instance, polyvinyl pyrrolidinone (PVP) can be prepared from

N-vinyl lactam in the presence of hydrogen peroxide in ammonia or water as solvent via radical polymerization reaction.[18]

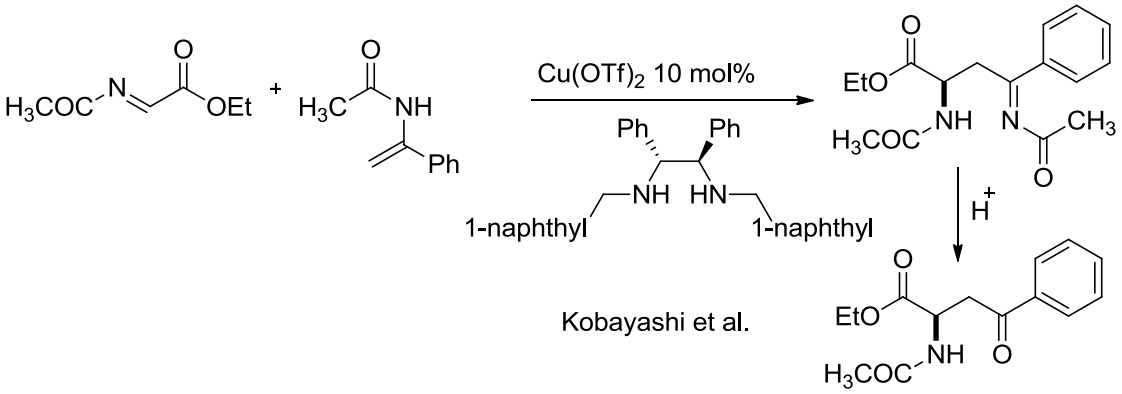
Figure 1: Enamide substructure in bioactive products.



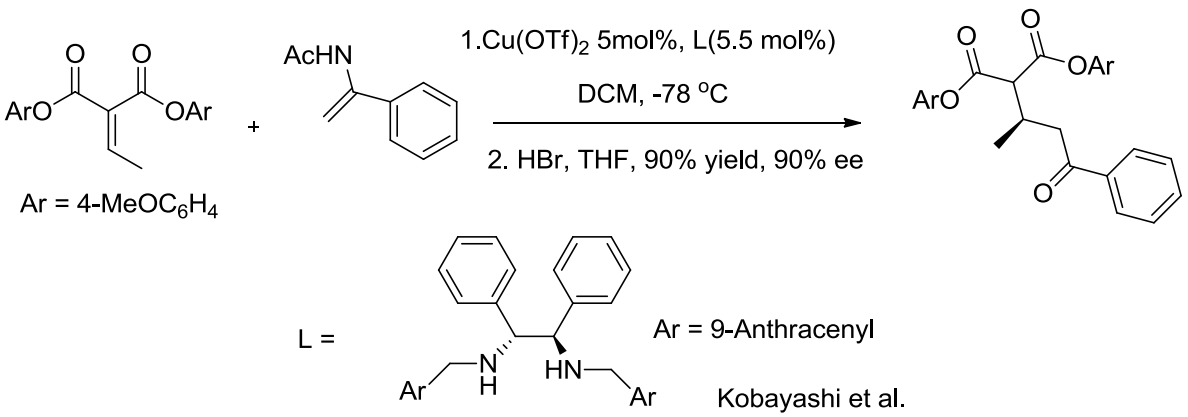
1.1.2 Enamides as nucleophiles

Enamides having a carbonyl group attached to nitrogen can be regarded as a masked enamine. Undoubtedly, the nucleophilicity of enamides is less than that of enamines, but still it is reactive enough to powerful electrophiles such as bromine, peracids, lead (IV) acetate etc. Kobayashi and his co-workers exploited the nucleophilicity of enamides in the copper-catalyzed enantioselective synthesis of amines from the reaction of enamides with *N*-acylimino esters (Scheme 2).[19] The same group also employed the enamides in enantioselective Michael reaction to form C-keto malonates (Scheme 3).[20]

Scheme 2

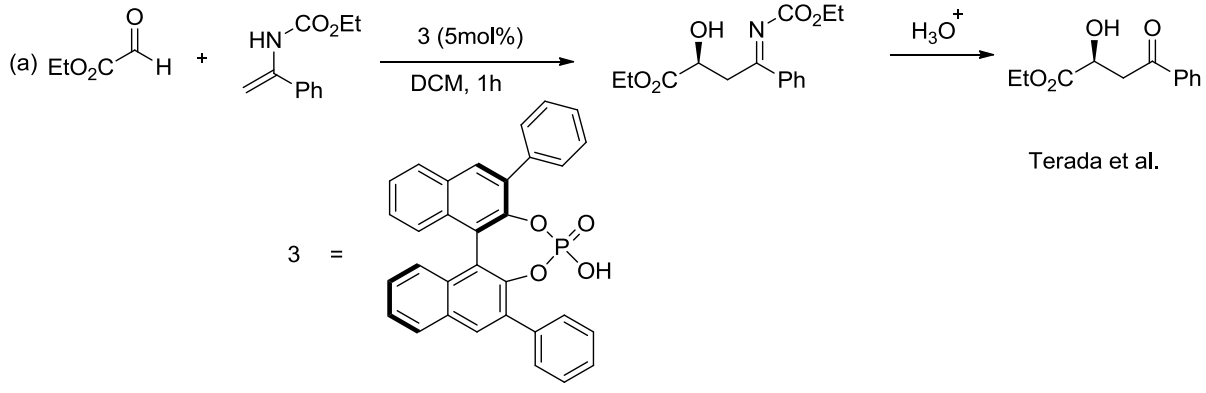


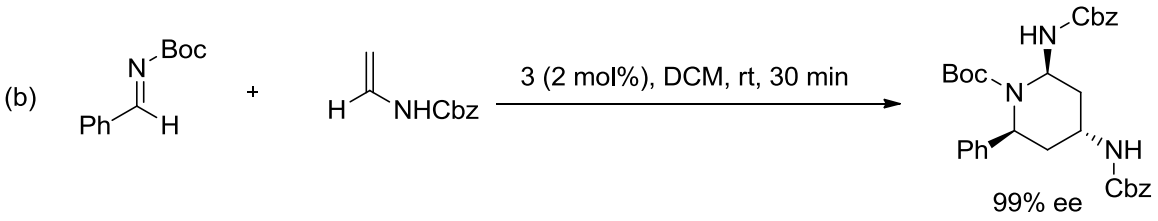
Scheme 3



Terada et al. reported enantioselective addition of enamides to glyoxal in the presence of Brønsted acid such as BINOL based phosphonic acids to produce β-hydroxy ketones enantioselectively (Scheme 4a).[21] Organocatalytic pathway of BINOL phosphonic acid catalyzes the enantioselective synthesis of piperidines using aldimine and enamide. In this case, it is expected that the β-amino imine product was formed from the Mannich reaction of enamide and imine, which undergoes subsequent nucleophilic attack by a second equivalent of enamide followed by cyclization to form the piperidine ring system with excellent enantioselectivity (Scheme 4b).[22]

Scheme 4

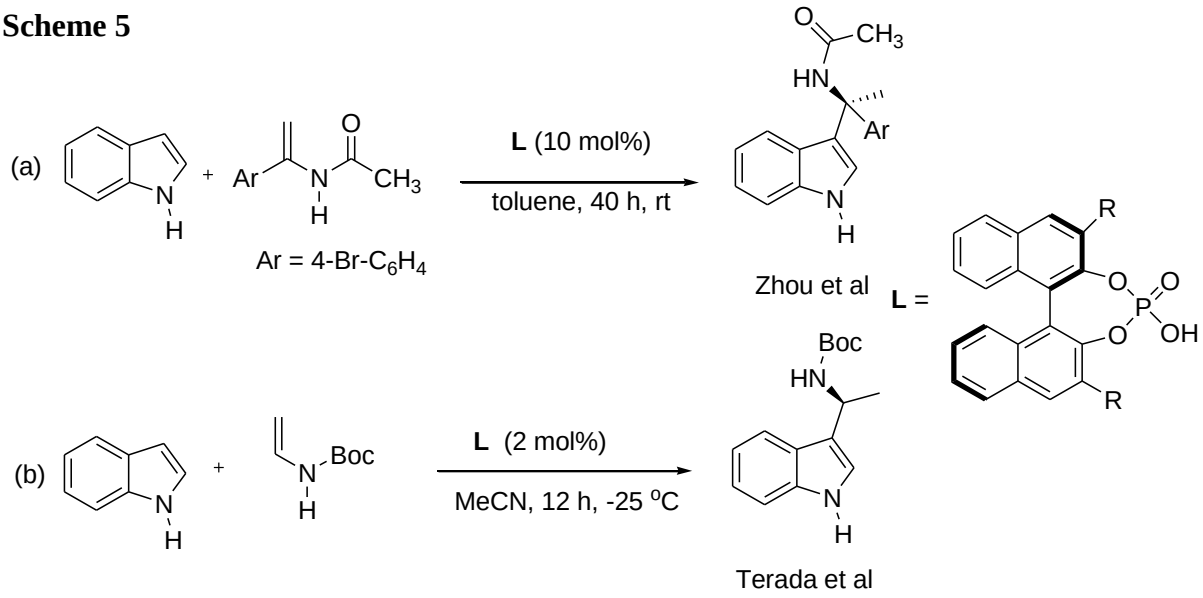




1.1.3 Enamides as electrophiles

The latent electrophilic nature of enamides was exploited by Terada and Zhao independently for the preparation of chiral amines. For instance, in 2007 Zhou and co-workers synthesized chiral tertiary amines with a quaternary carbon center using an enantioselective Friedel-Crafts reaction of indoles with α-aryl enamides in the presence of chiral Brønsted acids (Scheme 5a).[23] It has been reported that the chiral Brønsted acids promote the conversion of enamides to chiral iminium ion electrophiles, which can subsequently undergo in Friedel–Crafts reactions to generate the quaternary carbon centre (Scheme 5b).[24] The enamide is in equilibrium with the corresponding ketimine, which is activated upon protonation, so to accept nucleophilic attack of the indole from the *Re* face to afford the *(S)*-configuration of the stereocentre.

Scheme 5



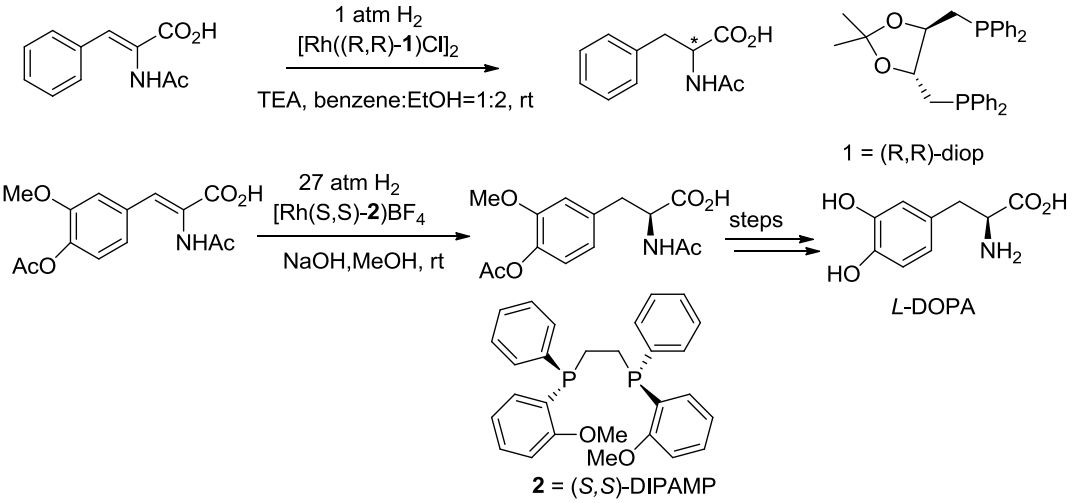
1.1.4 Enamides in transition metal catalyzed reactions

Since the pioneering works of Knowles[25] and Kagan[26] (Scheme 6) on enantioselective hydrogenation of *N*-acyl α-dehydroamino acids using rhodium complex, enamides are considered as a reliable and useful precursor for the synthesis of chiral amines as well as amino acids in the presence of transition metal catalyst. It is reported that the carbonyl protection of enamine is a prerequisite for achieving good enantioselectivity in the transition

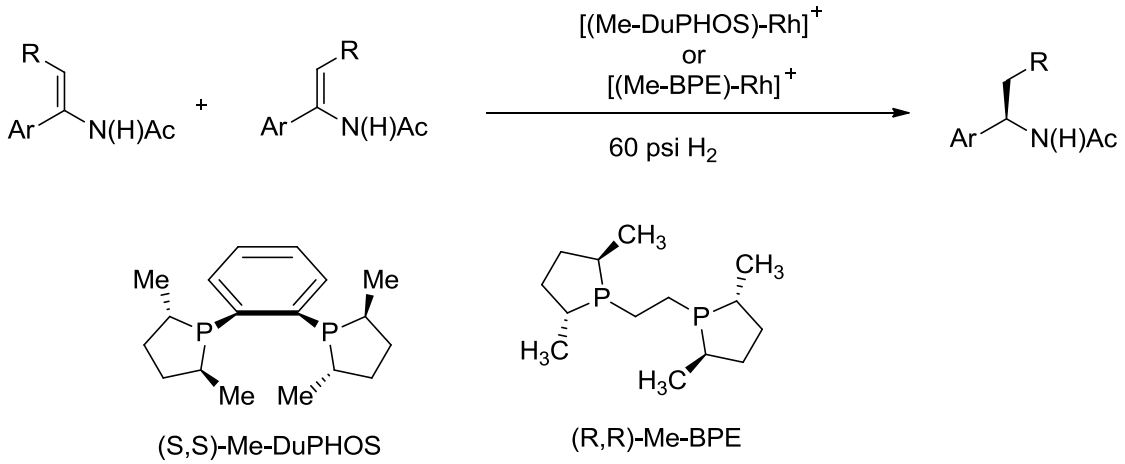
metal-catalyzed hydrogenation by forming a chelate complex with the metal of catalyst in the transition state.[8]

Furthermore, other ligands were also reported for the enantioselective hydrogenation of enamides. For instance, in 1996, Burk et al. used strong electron-donating DuPhos and BPE ligands for the hydrogenation of α-aryl enamides to produce chiral amides in the presence of Rhodium-catalyst (Scheme 7).[27]

Scheme 6

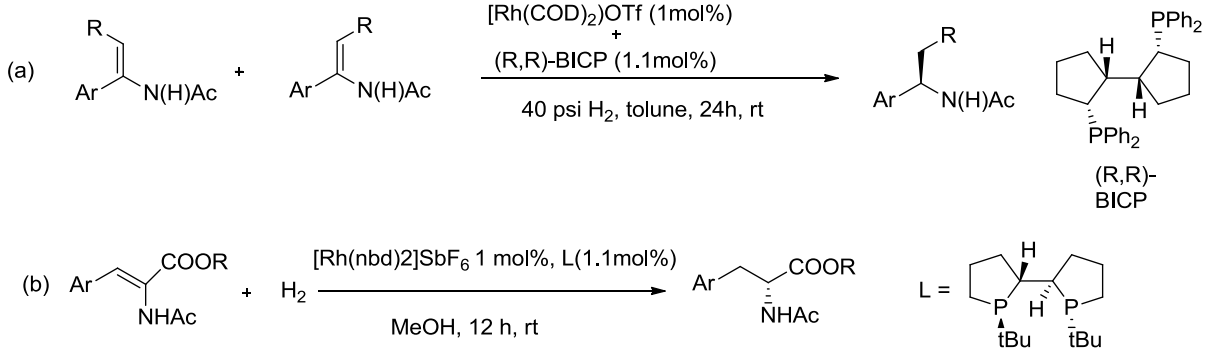


Scheme 7



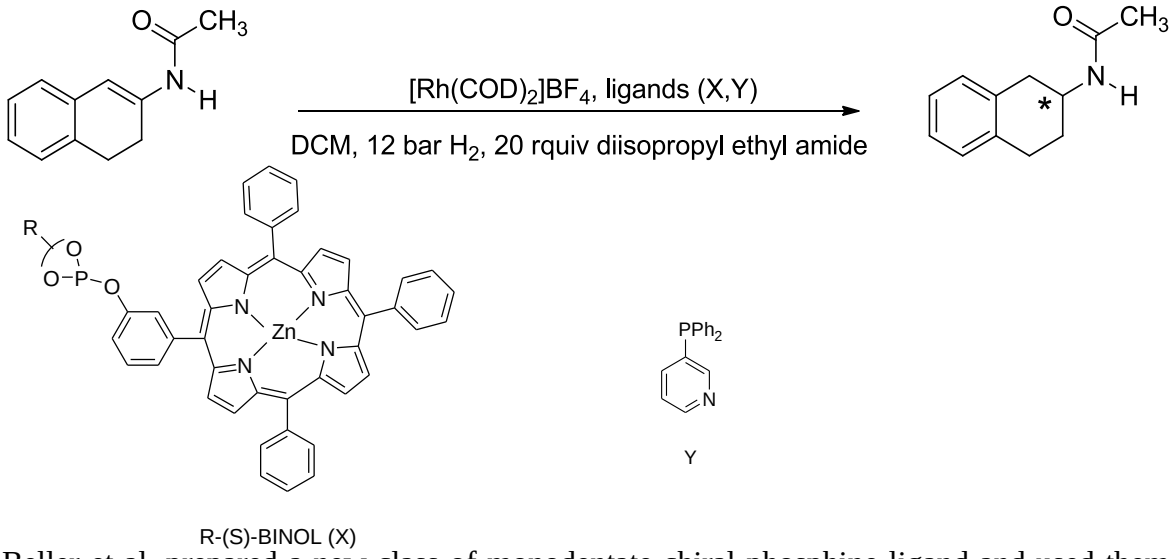
In 1998, Zhu and Zhang used BICP ligand for the rhodium-catalyzed asymmetric hydrogenation of α-substituted enamides to form enantiomerically enriched aryl alkyl amides (Scheme 8a).[28] In 2002, Tang and Zhang[29] reduced the double bond of enamide by rhodium catalyst that generated from $[Rh(nbd)_2]SbF_6$ in situ in the presence of TangPhos ligand (L) (Scheme 8b).

Scheme 8



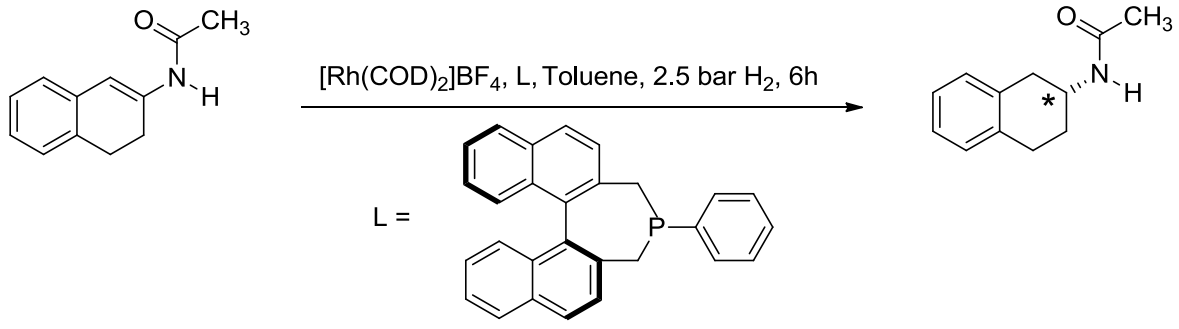
In 2006, Reek et al. reported the asymmetric hydrogenation of enamides in the presence of rhodium catalyst.[30] They have used supraphos ligands for the rhodium-catalyzed asymmetric hydrogenation of enamides. The combination of porphyrin-phosphite (X) and pyridyl phosphorus (Y) gave the best result for amine derivatives (Scheme 9).

Scheme 9



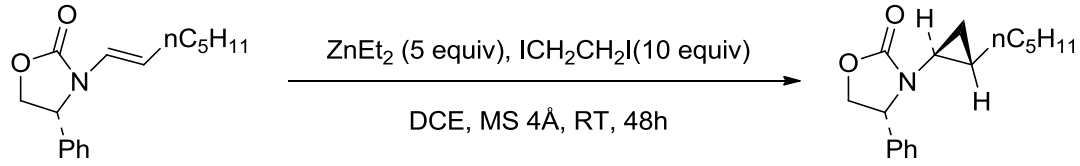
Beller et al. prepared a new class of monodentate chiral phosphine ligand and used them in the rhodium catalyzed hydrogenation of enamides (Scheme 10).[31]

Scheme 10



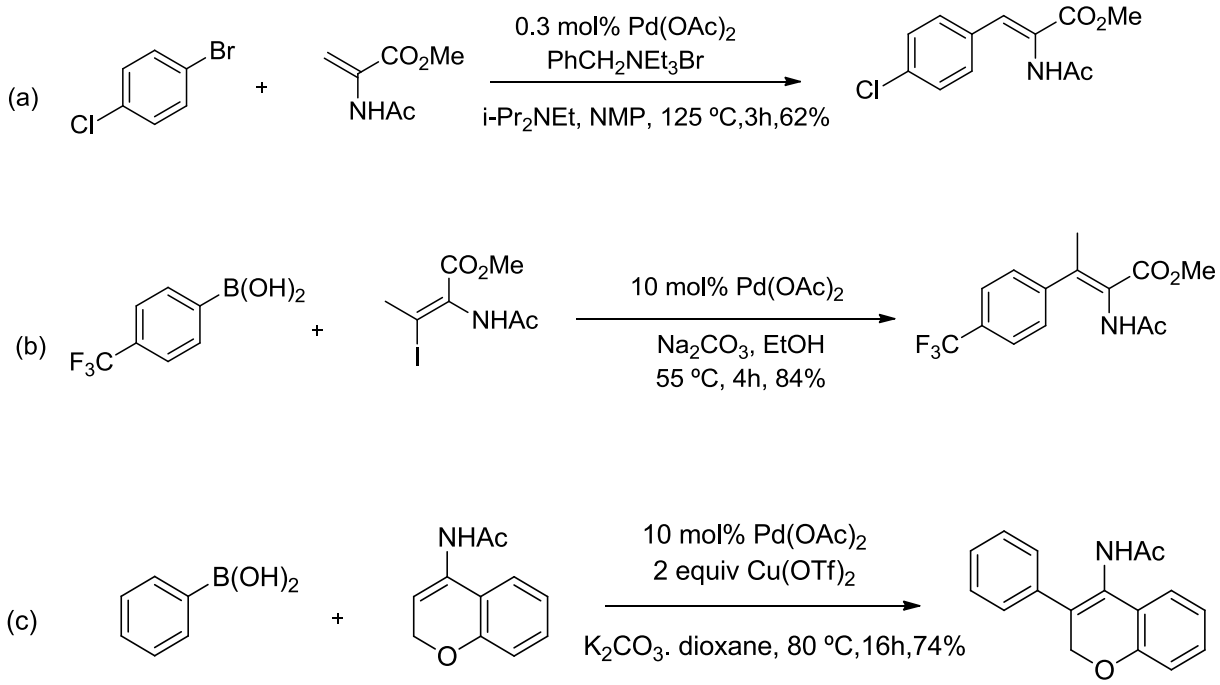
The tuneable nucleophilicity of the enamide makes it a promising substrate for cyclopropanation reaction. Hsung et al. reported the synthesis of chiral amino cyclopropanes from chiral enamides using Simmons-Smith reaction (Scheme 11).[32] They have conducted various reactions using different enamides and di haloalkanes as the methylidene source.

Scheme 11



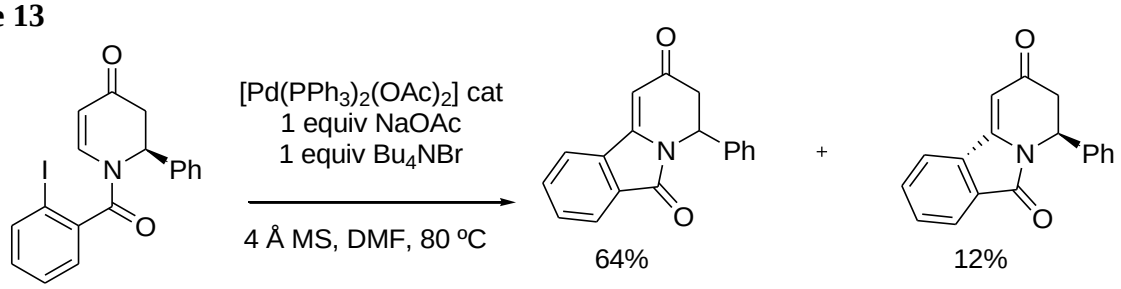
Moreover, enamides served as coupling partner for various coupling reactions such as Heck coupling,[33] Suzuki coupling[34] and C-H functionalization[35] to produced highly substituted enamides in the presence of Pd-based catalyst (Scheme 12).

Scheme 12



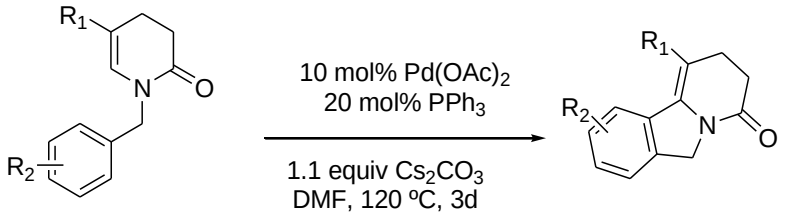
Intramolecular Pd-catalyzed coupling of enamides was also investigated. Zhang and co-workers reported the α-regioselective intramolecular Heck reaction of *N*-acyl-2, 3- dihydro-4-pyridinone which leads to heterocycles (Scheme 13).[36]

Scheme 13



Moreover, intramolecular cyclization of enamides was also achieved through Pd-catalyzed C-H activation. Evidently, Maier and co-workers[37] synthesized tricyclic isoindolines from the corresponding enamides (Scheme 14).

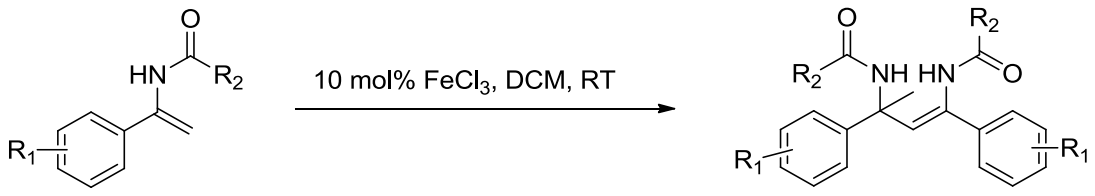
Scheme 14



R_1 = hexane, CH_2Ar, R_2 = H, OMe

In a recent communication, Guan et al. reported a $FeCl_3$-catalyzed self-condensation of acyclic enamides under very mild reaction conditions to produce nitrogen-containing quaternary carbon centres (Scheme 15).[38] The key step in this reaction is the nucleophilic addition of one equivalent of enamide to ketamine that generated from the isomerization of enamide under the reaction conditions.

Scheme 15

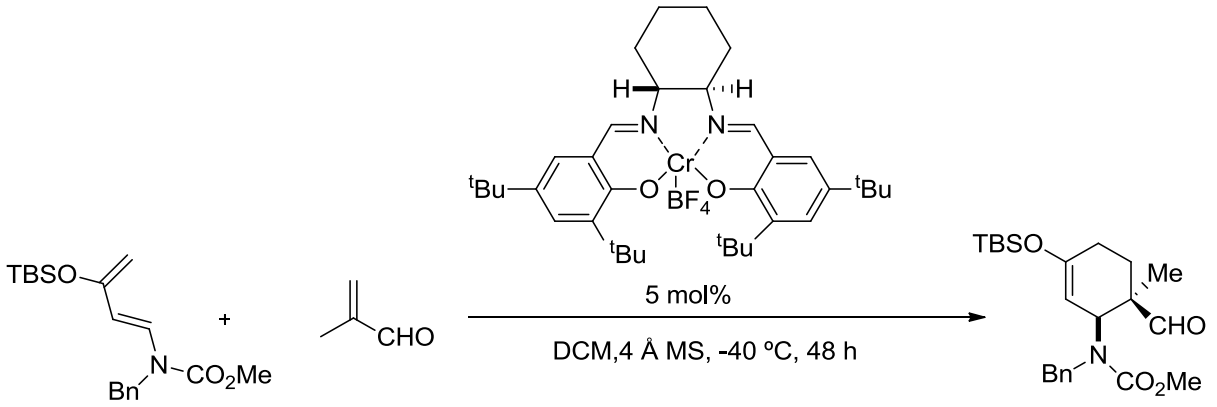


R_1 = alkyl, halogen, ether, NO_2
R_2 = COMe, COEt

1.1.5 Enamides in pericyclic reactions

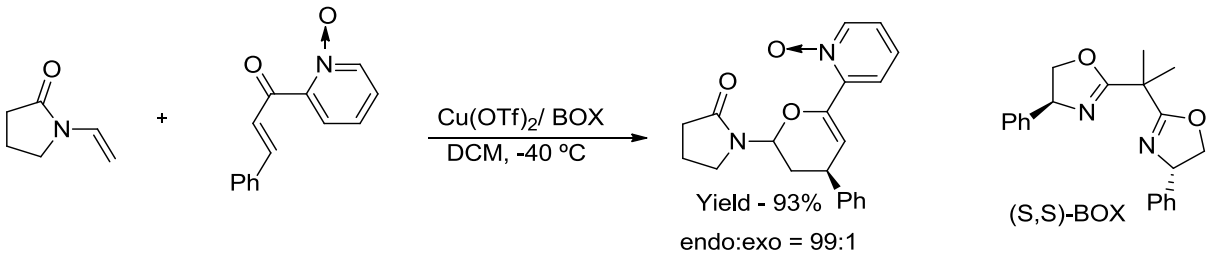
Enamides have been found to be use in pericyclic reactions for the preparation of nitrogen containing stereocenter. Rawal et al. employed conjugated enamides for the Diels-Alder reaction with the acrolein in the presence of Cr(III)-salen complex, to result synthetically useful cyclohexenyl carbamates with high enantiomeric excess (Scheme 16).[39]

Scheme 16



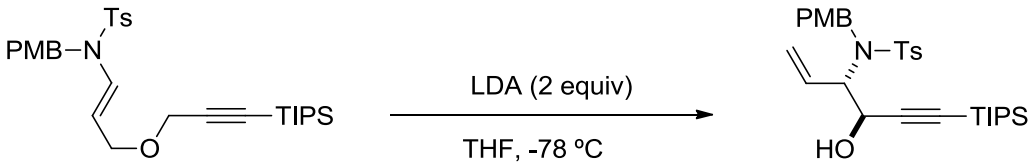
In 2009, Blay and co-workers described hetero Diels-Alder reaction of enamide and 2-alkenoylpyridine N-oxide in the presence of the copper catalyst and BOX to afford chiral dihydropyrans (Scheme 17).[40]

Scheme 17



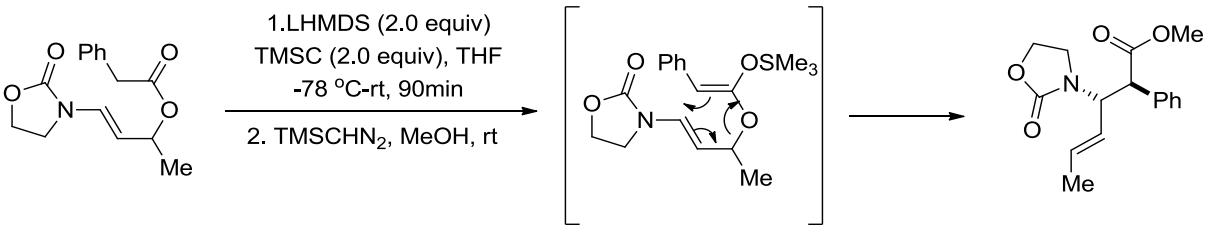
Sigmatropic rearrangement of enamides was first developed by Meyer, where base catalyzed [3,2]-Wittig rearrangement of enamides leads to the highly diastereoselective 1,2-amino alcohol derivatives (Scheme 18) in excellent yields.[41]

Scheme 18



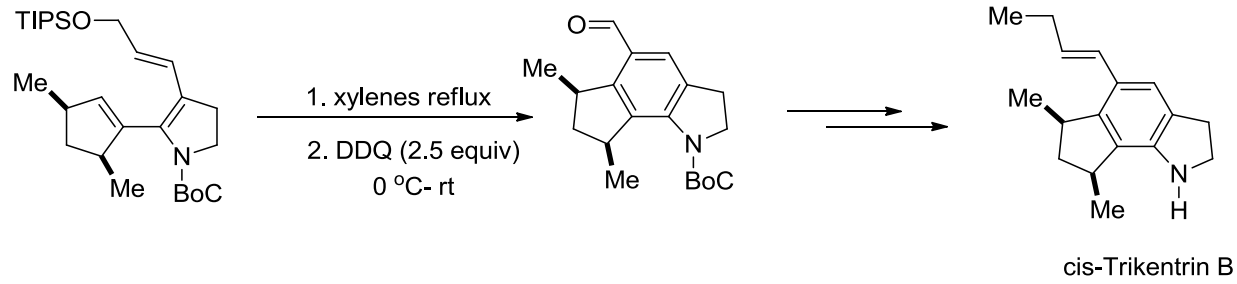
Carbery et al. also employed enamide substrates for the Ireland–Claisen [3,3]-rearrangement (Scheme 19) to produce β-amino acid derivatives.[42]

Scheme 19



Enamides are also successfully employed in electrocyclic reactions. For instance, Funk has utilized 2,3-pyrroline for thermal electrocyclic ring closure reaction (Scheme 20).[43] Similar strategy has been further extended towards the synthesis of welwistatin,[44] dragmacidin E[45] and nakadomarin A[46] natural product skeletons.

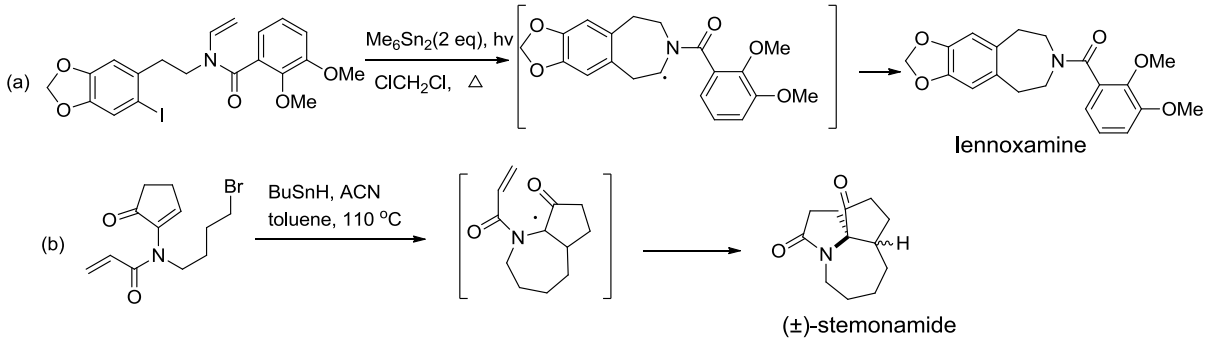
Scheme 20



1.1.6 Enamides in radical reactions

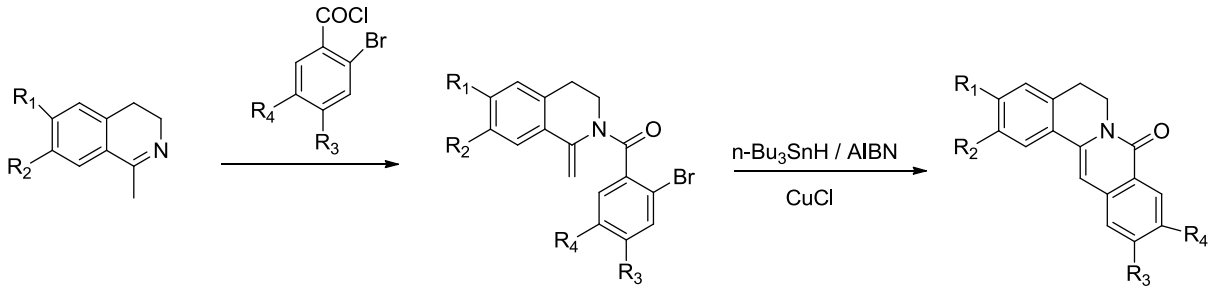
Enamides have also proven to be useful substrates in radical reactions. Reportedly, Ishibashi developed a short synthesis of lennoxamine via radical 7-endo cyclization of enamides (Scheme 21a).[47] The same group has also synthesized (±)-stemonamide from enamidein the presence of tributyl tinhydride (Scheme 21b).[48]

Scheme 21



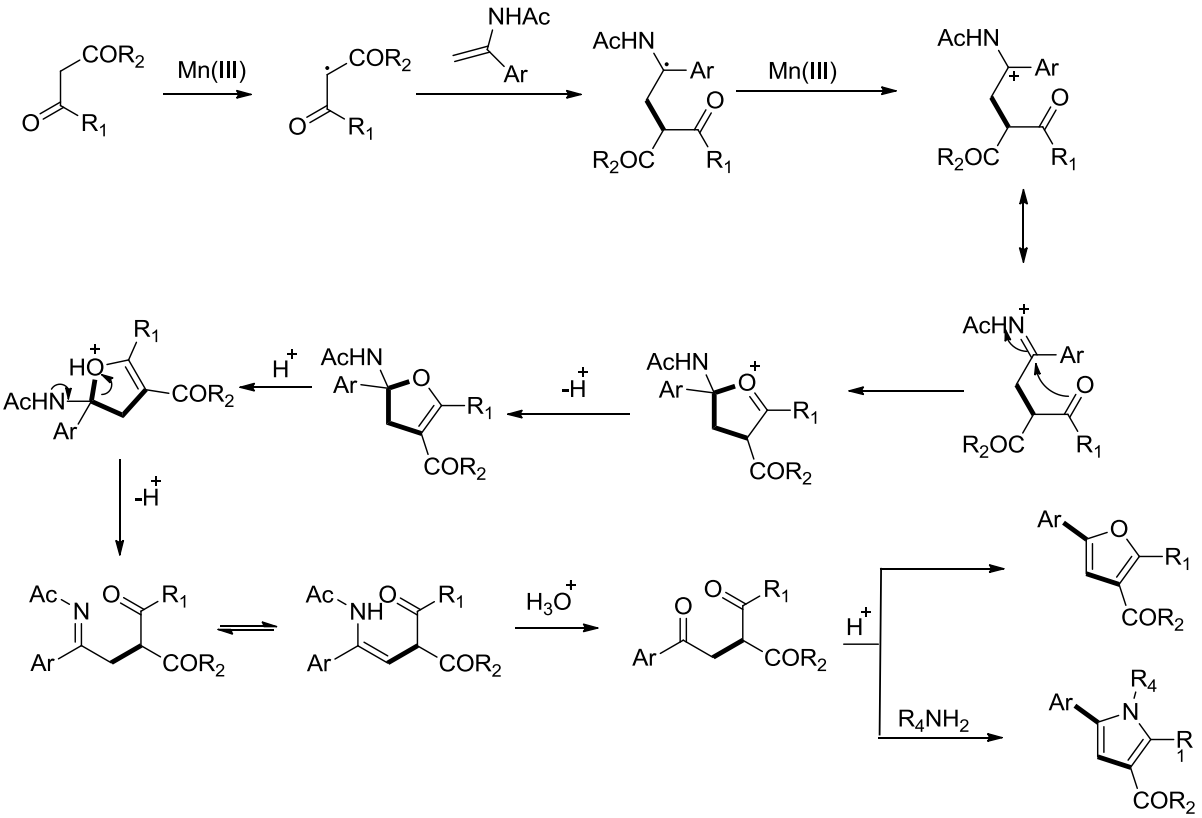
The oxoprotoberberine alkaloids were also synthesized efficiently by Lee et al. from the enamide derivatives by a radical-initiated cyclization reaction utilizing n-Bu_3SnH/AIBN and CuCl (Scheme 22).[49]

Scheme 22



An efficient manganese(III)-mediated oxidative coupling reaction between α-aryl enamides and 1,3-dicarbonyl compounds to produce dicarbonyl enamides was successfully developed by Li and co-workers[50] (Scheme 23). They proposed that the reaction proceed through the radical mechanism. Furthermore, it has been observed that the so formed dicarbonyl enamides undergo acid catalyzed cyclization to produce functionalized furans as well as pyrroles in good yield.

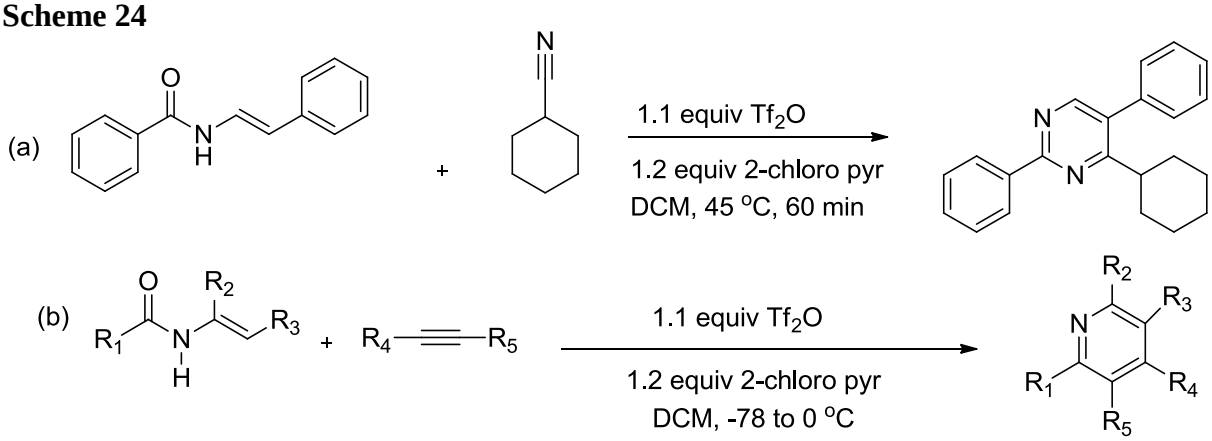
Scheme 23



1.1.7 Enamides in heterocycle synthesis

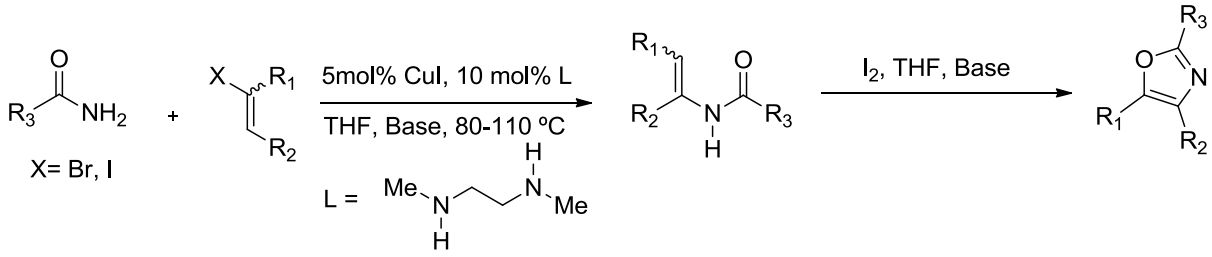
Enamides have been found extensive application in heterocycle synthesis. Notably, Movassaghi and Hill developed an efficient, single step route for the synthesis of pyrimidine derivatives from the reaction of enamides with nitriles using trifluoromethane sulfonic anhydride (Tf_2O) and 2-Chloro pyridine (Scheme 24a).[51] The same group also found application of the enamides for the synthesis of pyridine derivatives (Scheme 24b).[52]

Scheme 24



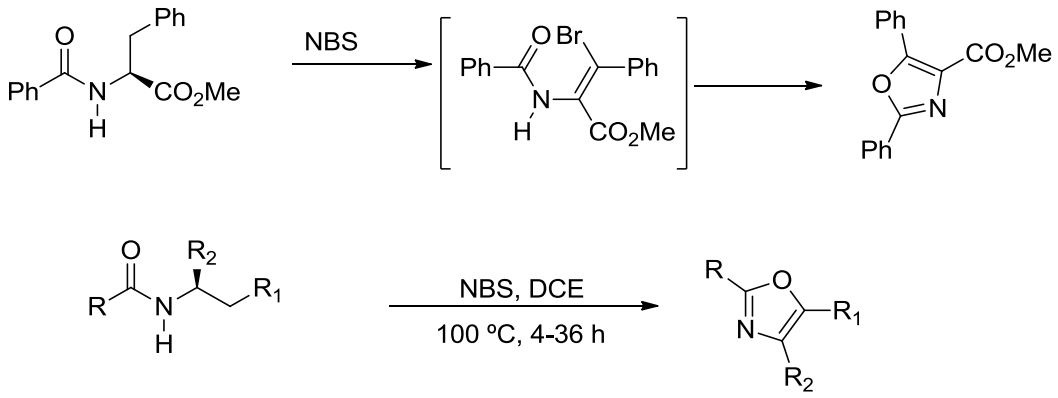
Enamides are also proved to be valuable substrate in oxazoles synthesis. In 2007, Buchwald et al. disclosed an interesting approach towards oxazole synthesis via copper catalyzed amidation of vinyl halides followed by intramolecular cyclization of enamides in the presence of iodine (Scheme 25).[53] In the same year, Glorius and co-workers described the copper catalyzed cyclization of β-haloenamide to produce oxazoles.[54]

Scheme 25



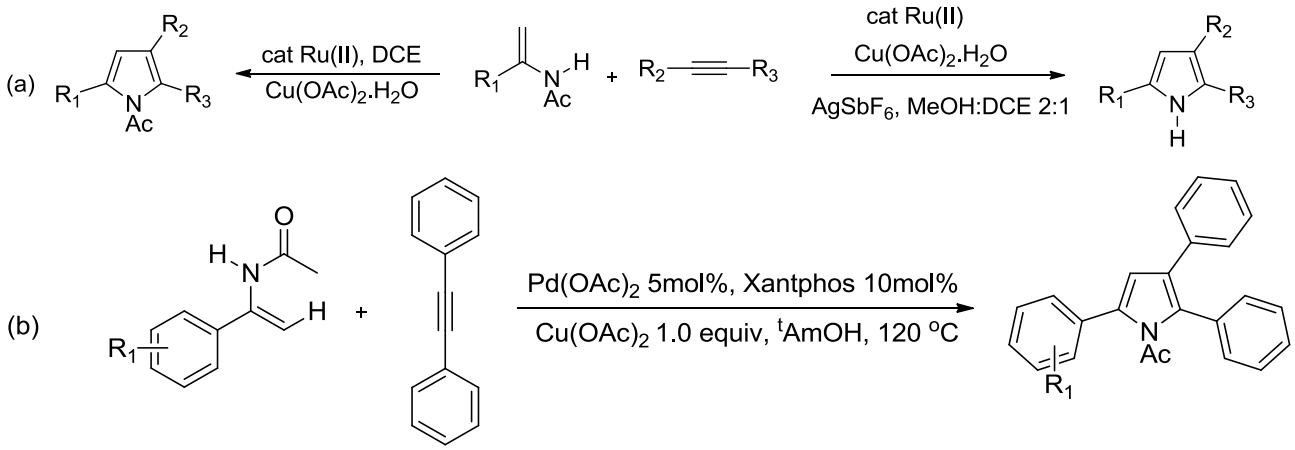
In 2010, Reissing and co-workers synthesized substituted oxazoles from the β-functionalized enamides in the presence of trifluoroaceticacid.[55] Recently, Bathula and his co-workers[56] synthesized substituted oxazoles from the *N*-acylated amino acid derivatives under metal-free conditions. Under their protocol, the β-bromoenamide was formed in-situ by bromination /debromination of *N*-acylated amino acid by NBS; which subsequently undergo cyclization at 100 ºC to produce di- and tri-substituted oxazoles (scheme 26).

Scheme 26



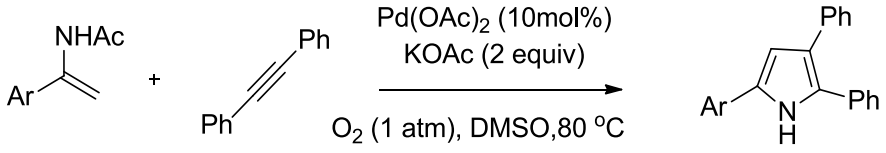
Enamides are also emerged as valuable substrates for the synthesis of substituted pyrroles using a transition-metal catalyst. For an interesting example, enamide react with substituted alkynes in the presence of Ru(II)-catalyst to produce substituted pyrroles (Scheme 27a).[57] Similar oxidative cyclization of enamides with alkyne also occurred in the presence of Pd-catalyst (Scheme 27b).[58]

Scheme 27



Very recently, Xu et al. reported the synthesis of substituted pyrroles from reaction of enamides and alkynes using 10 mol% palladium(II)acetate and molecular oxygen as an efficient, inexpensive oxidant for the Pd(II)/Pd(0) catalytic cycle (Scheme 28).[59]

Scheme 28



1.2 Methods for the Preparation of Enamides

Enamides have been synthesized from the following major approaches. These are

(i) *N*-acylation of enamines

(ii) Curtius rearrangement of α, β-unsaturated acyl azides

(iii) Olefination reactions

(iv) Condensation of amides with aldehydes

(v) Transition metal catalyzed the isomerization of *N*-allylated amides.

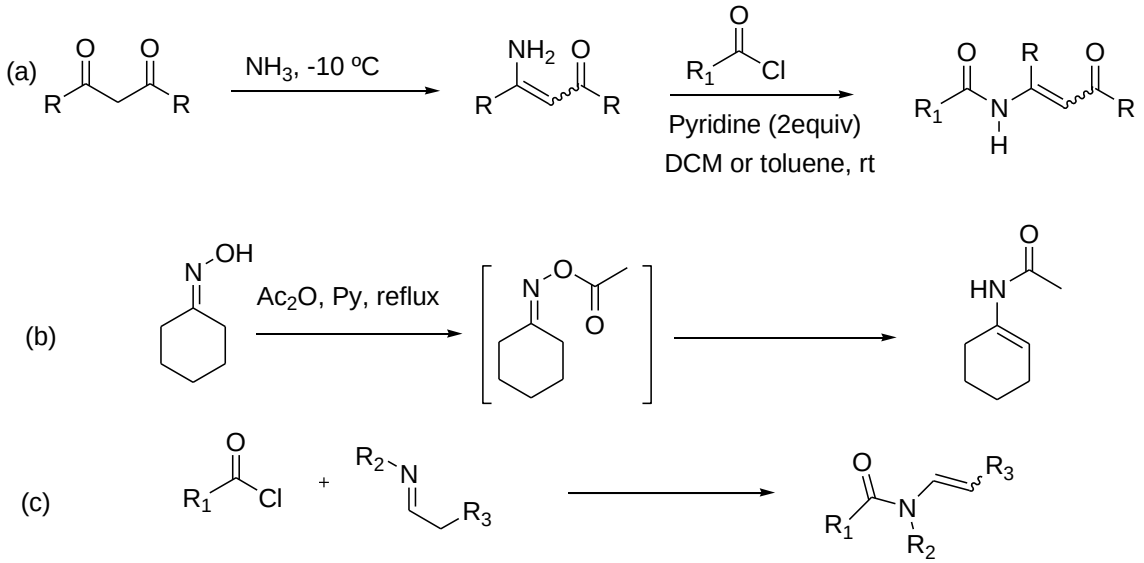
(vi) C-N bond formation using transition metal catalyzed cross coupling of amides and vinyl derivatives

A brief discussion on enamide synthesis using above methods is here and under.

1.2.1 *N*-acylation of enamines

Surrogating enamines by acid chloride is the simplest and probably the most general method to achieve enamides. Enamines may be achieved by the reaction of 1, 3-dicarbonyl compounds with ammonia or its precursor (Scheme 29a). Treatment of ketoximes with pyridine and acetic anhydride under reflux conditions also produce enamides (Scheme29b).[60] Later, a phosphine-mediated reductive acylation of oximes was reported to furnish enamides in good yields (up to 89%). Moreover, imines were also functionalized to enamides by treatment with acid chloride (Scheme 29c).[61]

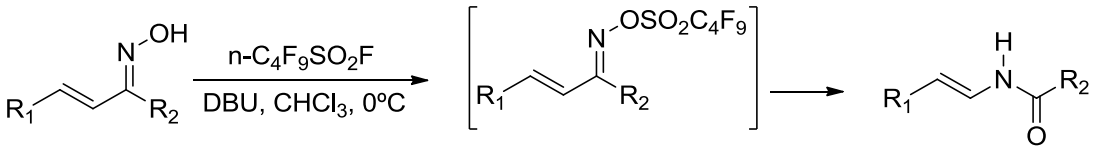
Scheme 29



Recently, Yan et al. developed a method for the synthesis of enamides (Scheme 30)[62] from the reaction of α, β-unsaturated ketoximes and fluoroalkanosulfonyl fluorides in the presence of DBU. They proposed that the fluorinated reagent act as an activator for the

removal of -OH group; and hence Beckmann rearrangement proceeds smoothly even at room temperature to produce acid sensitive enamides. Notably, metal-catalyzed version of such rearrangement to produce enamides is not well precedented.

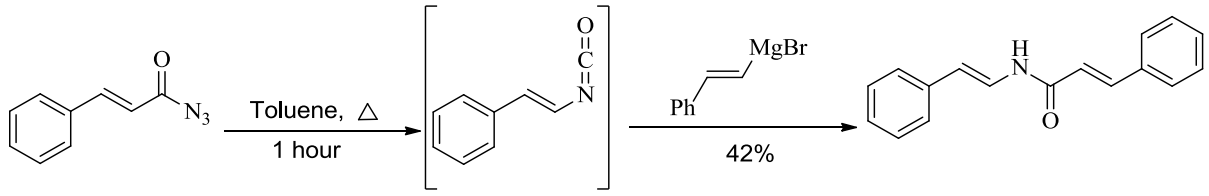
Scheme 30



1.2.2 Curtius rearrangement of α, β-unsaturated acyl azides

Curtius reaction was reported to be useful for enamide synthesis. When α,β-unsaturated azides undergo Curtius rearrangement, isocyanate forms, which on treatment aryl or vinyl or alkyl nucleophiles leads to the enamide. Here, the geometry of the enamides solely depends on the geometry of the azide taken for the reaction. Evidently, Tayler et al. prepared *E*-enamides from the reaction of α,β-unsaturated isocyanate with styryl magnesium bromide in moderate yield (Scheme 31).[63]

Scheme 31

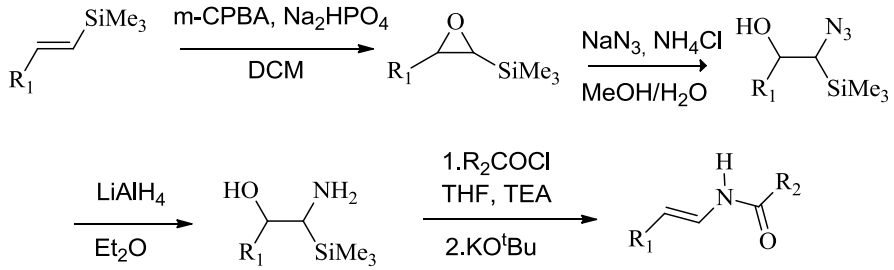


1.2.3 Olefination reactions

Peterson olefination reaction

Peterson reaction of β-hydroxy α-salilamides is also emerged as a selective method to generate *E*- or *Z*-enamides. For an interesting example, Furstner et al. described the stereoselective synthesis of *E*-enamides under basic condition. They employed multi-step synthesis to achieve β-hydroxy α-salilamides. The starting material was prepared from the epoxidation of vinyl silane, followed by ring opening, reduction and subsequent *N*-acylation reaction (Scheme 32). This method was also found to be suitable to produce *E* or *Z*-enamides depending upon the geometry of the starting material.[64]

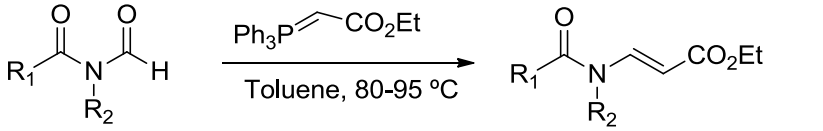
Scheme 32



Wittig-type olefination reactions

The Reaction of Wittig-reagent with *N*-formyl amide represents a straight forward route to access enamides. In this regard Marquez et al. prepared enamides from the Wittig-type olefination reaction of amide and lactam (Scheme 33).[15]

Scheme 33

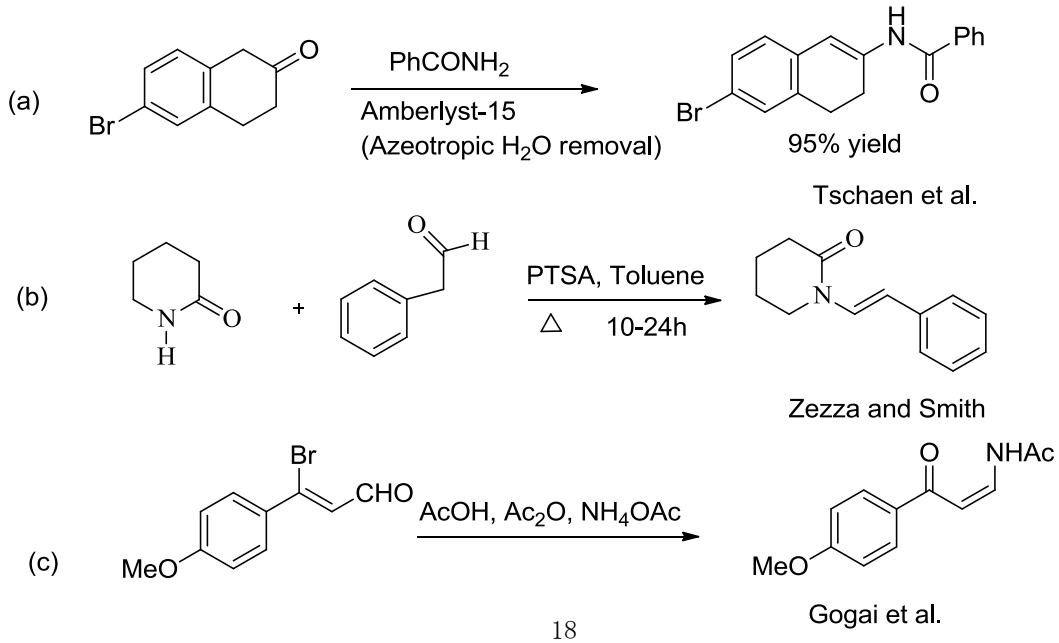


Marquez et al.

1.2.4 Acid catalyzed condensation of amides with aldehydes/ketones

Tschaen et al. synthesized enamides from the reaction of amide with ketone in toluene in the presence of amberlyst-15 with azeotropic removal of water (Scheme 34a).[60] Zezza and Smith described the synthesis of *E*-enamides from the condensation of amides with aldehydes in the presence of catalytic amount of 4-toluenesulfonic acid (Scheme 34b).[65] Very recently, Gogai et al. described the synthesis of β-ketoenamides from β-halo α,β-unsaturated aldehydes using ammonium acetate, acetic acid and acetic anhydride (Scheme 34c).[66]

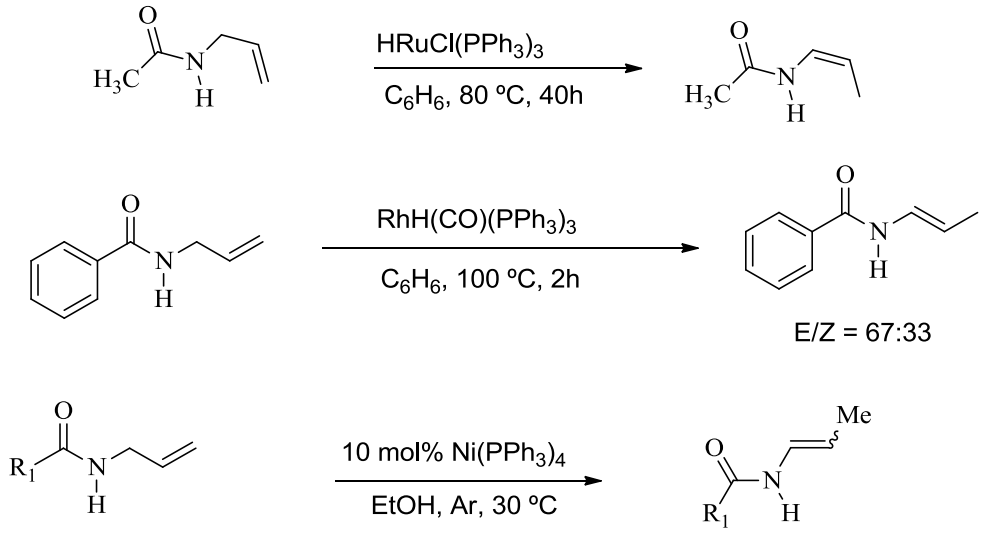
Scheme 34



1.2.5 Transition metal catalyzed isomerization of *N*-allylated amides

Isomerisation of *N*-allylamides in the presence of transition metal catalysts such as Fe, Rh and the Ru-based catalyst is an important approach to achieving enamides. Interestingly, the migration of double bond occurs by the rhodium or ruthenium hydrides. However, this method is lacking stereoselectivity producing the mixture of *E*/*Z*-isomeric mixture of enamides. Very recently, Wang et al. used $Ni(PPh_3)_4$ as the catalyst for the isomerization of *N*-allyl amide to afford enamides (Scheme 35).[67]

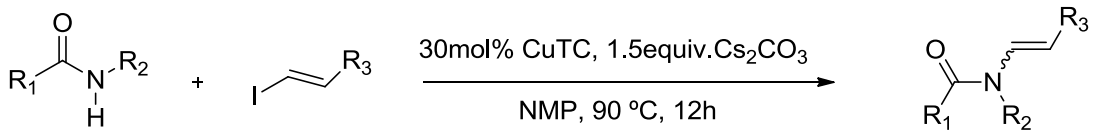
Scheme 35



1.2.6 Transition metal catalyzed cross coupling of amides and vinyl derivatives

Transition metal catalyzed *N*-alkenylation of amides considered to be a potential route to access enamides. In recent years, Cu and Pd-catalysts were predominantly used to access enamides through cross-coupling reactions. For instance, Porco and Shen reported the cross-coupling of amides with vinyl iodides in the presence of copper(I) carboxylate to achieve *E*/*Z* enamides in moderate to good yield (Scheme 36).[68] This method has wide substrate scope although having with lack of selectivity.

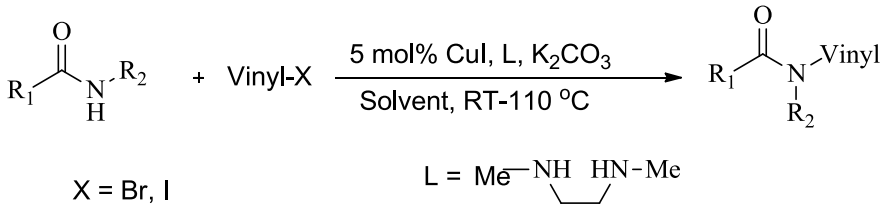
Scheme 36



Buchwald and co-workers developed a general and efficient ligand assisted copper catalyzed amidation reaction of vinyl iodide and bromides to afford enamides.[69] This method proved to be very successful with substrates bearing ester, silyl ether and amino groups (Scheme 37).

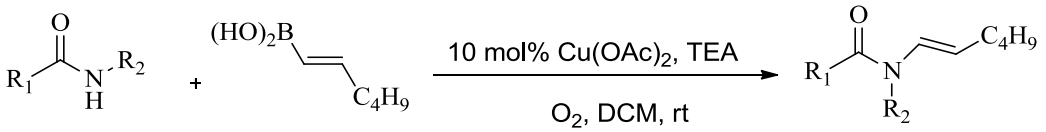
They observed that the geometry of double bond of the vinyl halides remains unaltered under the reaction conditions.

Scheme 37



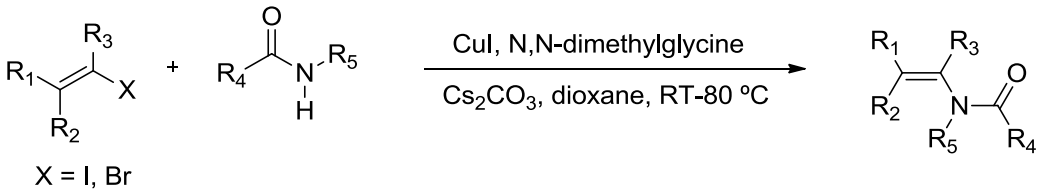
Later, Lam and co-workers reported the copper-catalyzed amidation reaction through the C-N cross-coupling of amides with vinyl boronic acids under mild reaction conditions (Scheme 38).[70]

Scheme 38



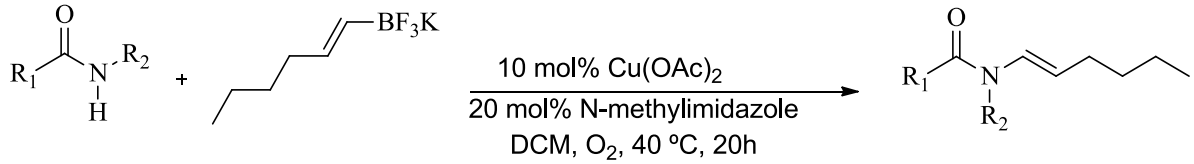
Ma and co-workers also used *N*,*N*-dimethylglycine as an efficient ligand for CuI-catalyzed cross coupling of amides or carbamates with vinyl halides to produce C-N bond. Moreover, the stereochemistry of enamides is largely dependent on the nature of the vinyl halide (Scheme 39).[71]

Scheme 39



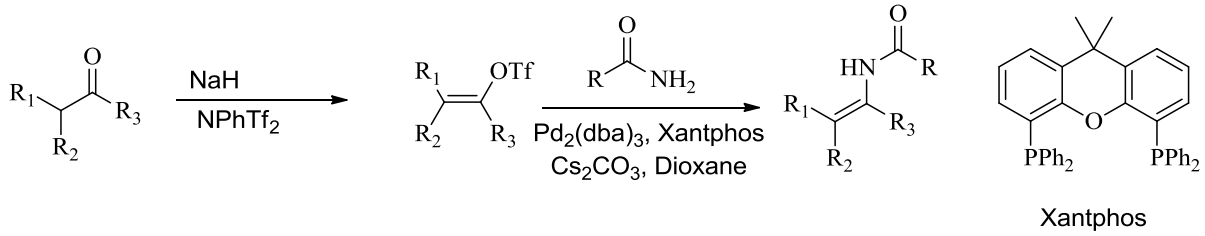
Another copper-catalyzed stereoselective methodology for the synthesis of *E*-enamides was developed by Batey and his co-workers (Scheme 40). They used $Cu(OAc)_2$ as catalyst for the cross coupling of amides with potassium alkenyl trifluoroborates in the presence of *N*-methylimidazole ligand.[72]

Scheme 40



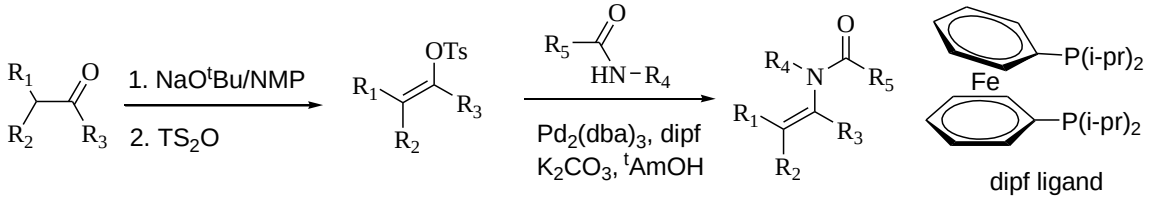
Besides, Pd-catalysts were also competently used for *N*-alkenylation of amides to produce enamides. Wallace et al. exploited the higher reactivity of vinyl triflates over bromide for the Pd- catalyzed cross-coupling with amide in the presence of xantphos to produce enamide (Scheme 41).[73]

Scheme 41



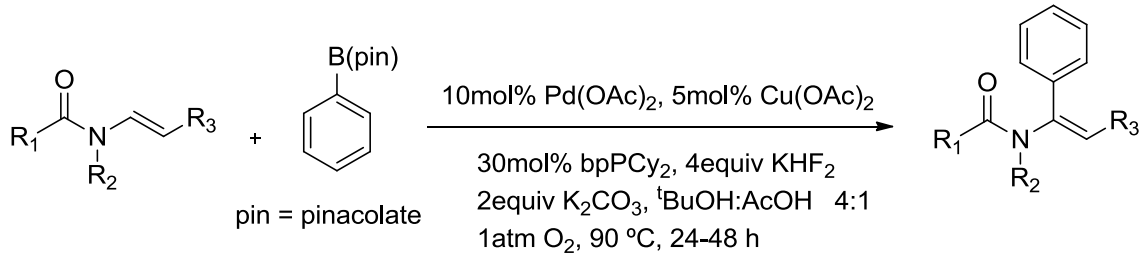
Furthermore, Klapers et al. introduced less expensive and easily isolable enol tosylates as a coupling partner for the synthesis of functionalized tri- and tetra-substituted enamides (Scheme 42).[74] They have prepared vinyl tosylates from the reaction of ketones with Ts_2O in the presence of NaO^tBu /NMP. $Pd_2(dba)_3$ along with ligand dipf was used for the cross-coupling of amides with less hindered ring tosylates to produce enamides.

Scheme 42



In 2011, Liu et al. reported the stereoselective synthesis of highly substituted enamides using palladium and copper co-catalytic system. 2-(Dicyclohexylphosphino)biphenyl ($bpPCy_2$) was used as ligand to promote the reaction in the presence of K_2CO_3 in a mixture of solvents ^tBuOH : AcOH = 4:1 (Scheme 43).[75]

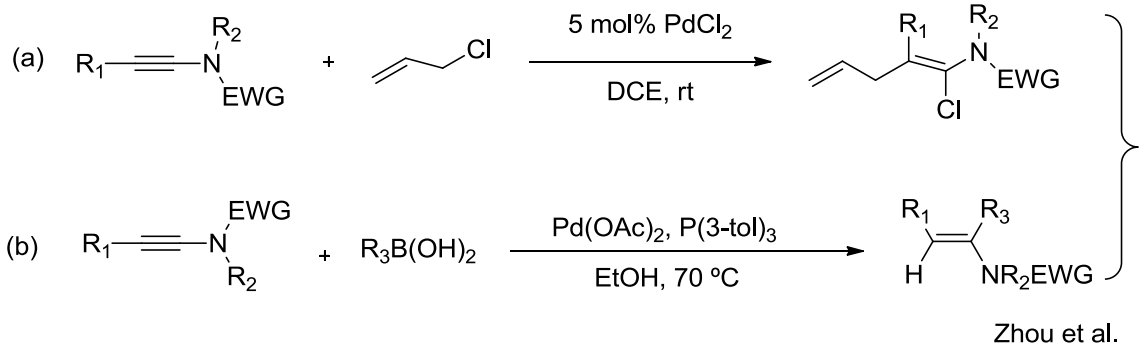
Scheme 43



Considering the cost and availability of olefins, Pd-catalyzed oxidative amidation of alkenes may be presumed as a promising and challenging method to produce enamides. Moreover, Use of unfunctionalized alkene as a coupling partner to achieve enamides has relatively less literature precedent. As our present work is closely related to oxidative amidation reaction, detailed discussion on the same will be presented in Chapter 2.

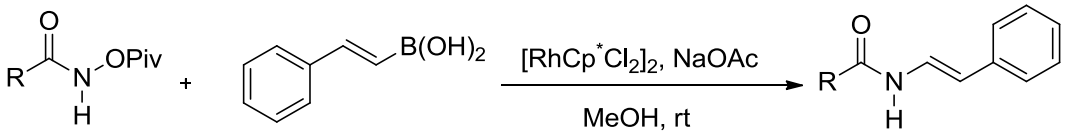
Additionally, ynamides are also treated as an important precursor to produce enamides. Some of the important reactions in this context are presented as follows. In 2011, Zhu et al. proposed an atom economic approach to access multi substituted enamides from the palladium catalyzed chloroallylation of ynamides (Scheme 44a).[76] Furthermore, very recently, the same group reported the Pd- catalyzed cross-coupling of ynamides with boronic acid derivatives to produce α,β-disubstituted enamides in the presence of tritolyl phosphine (Scheme 44b).[77]

Scheme 44



Besides, Rh-catalysts are also employed successfully for *N*-alkenylation of amides (Scheme 45). For instance, Loh et al. developed Rh(III)-catalyzed umpolung amidation of alkenyl boronic acids for the synthesis of enamides. This reaction proceeds readily at room temperature and displays a wide spectrum of functional group tolerance.[78] This method involves the hydroboration of alkynes to produce vinyl boronic acid, which subsequently undergo *N*-alkenylation to produce *E*-enamides selectively.

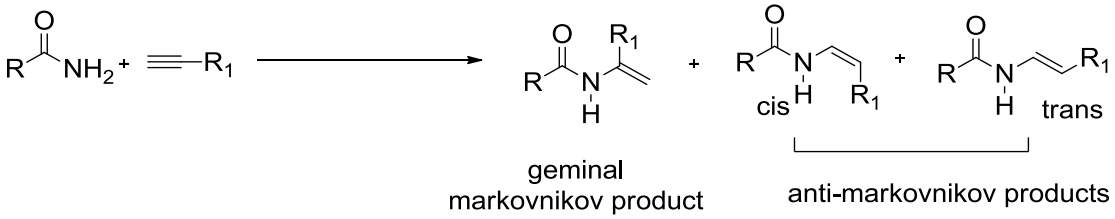
Scheme 45



An addition of amides to terminal alkynes, known as hydroamidation, is an atom-economic and convenient methodology for the synthesis of enamides. Such addition could

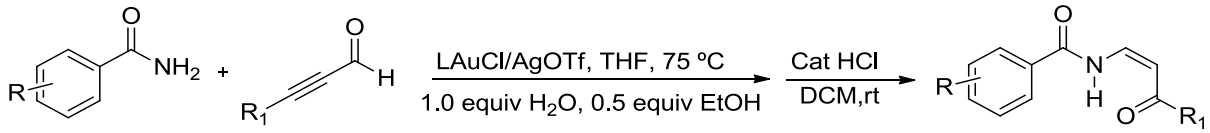
afford a mixture of three possible adducts, one Markovnikov's product and two anti-Markovnikov's products (*E* and *Z*-isomer) (Scheme 46).

Scheme 46



Hong et al. described the gold complex mediated hydroamidation of substituted propynal to produce enamides. Interestingly, in this reaction the stereochemistry of the product largely depends on the nature of the solvent (Scheme 47).[79] Several other examples are also precedent till data in the literature using Rh-, Ru- and Re-based catalyst. As our present work is based on the hydroamidation of alkyne to produce enamides, the details are discussed in Chapter 3.

Scheme 47



1.3 Objectives

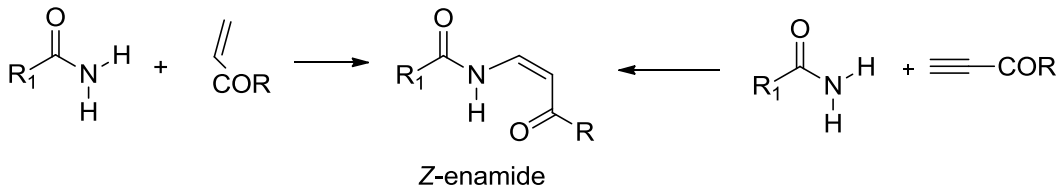
Inspite of significant development on oxidative amidation reaction to achive enamides, there are still some limitations. For instance, the transition metal catalysed protocols involving the coupling of amides with olefins often result in the thermodynamically more stable *E*-enamide predominantly. However, access to thermodynamically disfavoured *Z*-enamide is relatively difficult and hence more challenging. Indeed, the stereoselective synthesis of such *Z*-enamides is less endowed with literature precedent.

Hydroamidation of alkynes has been emerged as another alternative to access enamides. Pioneering work in this line has been carried out by Gooβen and his co-workers. They reported that Ru-complexes catalyze the reaction to produce enamides (*E* and *Z*) selectively. However, the selectivity is largely dependent on the nature of the ligand used. Other catalysts involving transition metals such as Ru, Re and Au were also employed to produce enamides. On the other hand, inspite of immense use of Pd-catalysts in different types of C-C and C-heteroatom cross-coupling reactions, there is no use of Pd-catalyst for

hydroamidation of alkyne to produce enamides. In order to address the above challenges, we define our present objective as follows (Scheme 48):

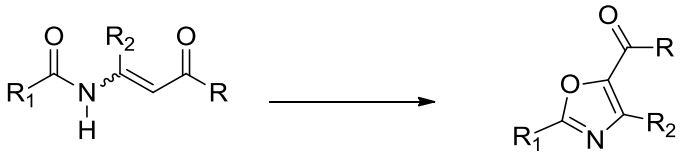
1. Transition metal catalyzed stereoselective synthesis of enamides from oxidative amidation of alkenes
2. Pd-catalyzed hydroamidation of alkynes to produce enamides stereoselectively

Scheme 48



Additionally, we also wish to demonstrate the use of enamides in heterocycle such as oxazole synthesis (Scheme 49).

Scheme 49



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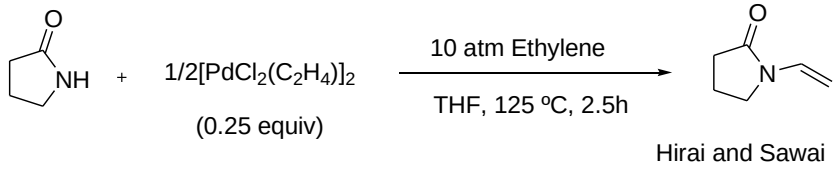
Chapter-2

Stereoselective Synthesis of Enamides by Palladium-catalyzed OxidativeAmidation of Alkenes

2.1 Introduction

In addition to the conventional methods, Pd- and/or Cu-catalyzed cross-coupling of vinyl derivatives (viz., halides,triflates, tosylates, borates) with amides have been employed to access a wide range enamides (see the previous chapter). However, these methods often require rigorous conditions, such as exclusion of moisture and air, elevated temperature, and utilization of the excess strong base.[1]The proper functionalization of the coupling partner (i.e., vinyl substrate) often suffers from low yield or intricacy in preparation. The stereocontrol of the double bond presents another potential problem, particularly in the synthesis of thermodynamically disfavoured *Z*-enamides. Thus, it is highly desirable to develop general and practical methods for the stereoselective preparation of enamides, using simple and readily available vinyl substrates. Evidently, direct oxidative amidation of the olefins have been exploited as a possible alternative to overcome these limitations, and indeed, some elegant methods have been disclosed along this line. For instance, Hirai and Sawai reported the coupling reaction of cyclic amides with ethylene-palladium chloride complex to produce enamides (Scheme 1).[2] This reaction proceeds through the migratory insertion of nitrogen nucleophile followed by reductive elimination step to produce *N*-vinyl amides in moderate to good yield.

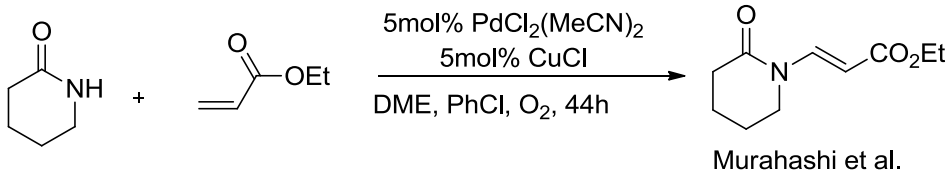
Scheme 1



Hirai and Sawai

In 1992, Murahashi and co-workers revealed the $PdCl_2(MeCN)_2$-catalyzed amidation of electron deficient olefins to produce enamides. They found that encarbamate were more reactive than the cyclic amides in C-N cross-coupling reaction (Scheme 2).[3] They used CuCl as co-catalyst in the presence of oxygen to complete the catalytic cycle. Stahl and co-workers also described the Palladium catalysed aerobic oxidative amidation of alkenes. Their protocol is found to suitable for the formation of *N*- unactivated alkenes bond via vinyl transfer from vinyl ethers (Scheme 3a). The proposed mechanism involves the formation of π-complex with olefin, which subsequently undergo migratory insertion to form σ-complex (Scheme 3b). Their protocol is also found to be effective for the cross coupling of tosylamides with vinyl ethers.[4]

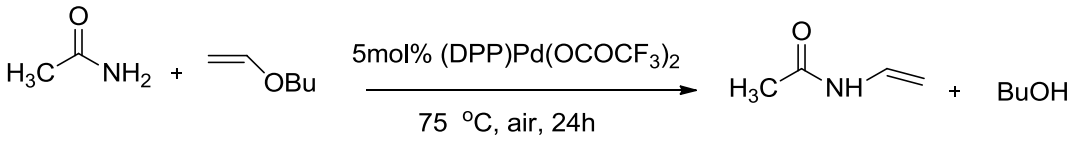
Scheme 2



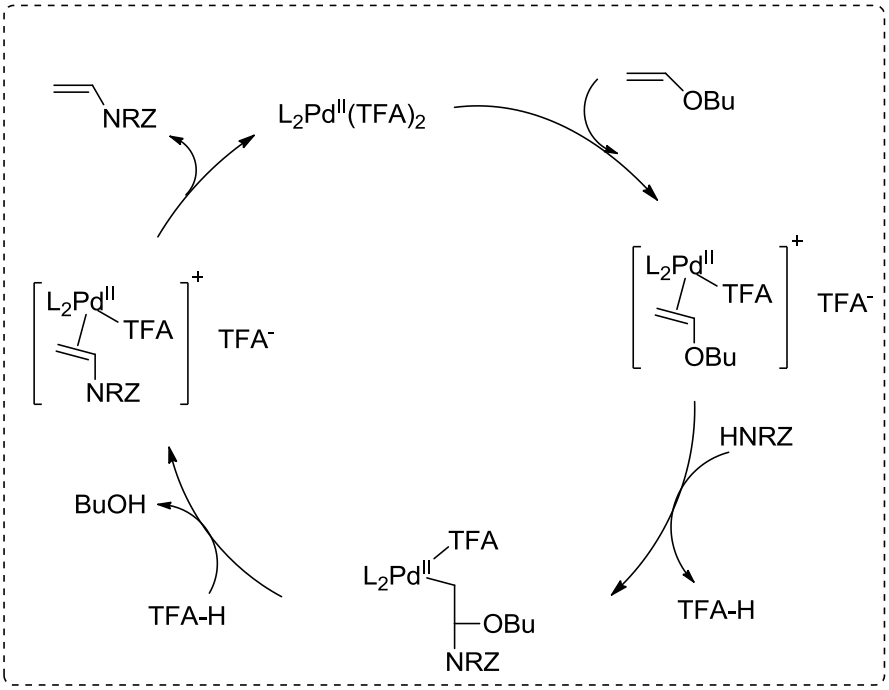
Murahashi et al.

Scheme 3

(a)

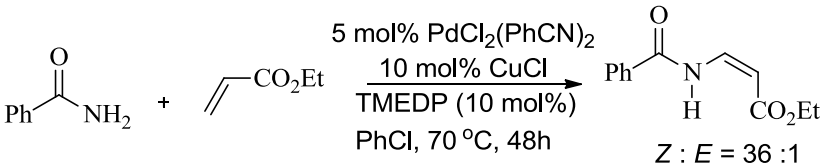


(b)



Chang et al. also contributed a Pd/Cu-catalyzed protocol for the selective synthesis of *Z*-enamide from the acyclic amides (Scheme 4).[5] They observed that certain additive like phosphonates and phosphine oxides increased the reaction rate in non-polar solvents under oxygen atmosphere. A wide range of primary amides was also reacted with electron deficient olefins.

Scheme 4

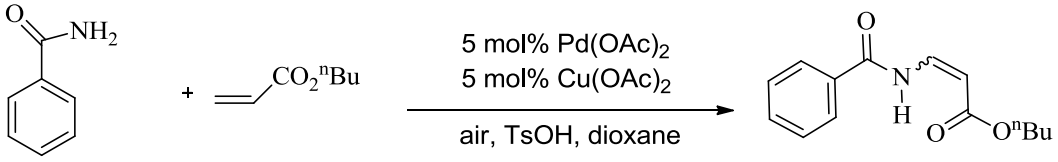


Z : *E* = 36 :1

Chang et al.

Morerecently, Liu and Hii reported a chloride-free, Pd/Cu co-catalyzed system for the cross-coupling of olefins with electron rich amides. They developed a new catalytic system that allows the synthesis of enamides from easily available nitrogen nucleophiles and activated olefins (Scheme 5).[6]

Scheme 5



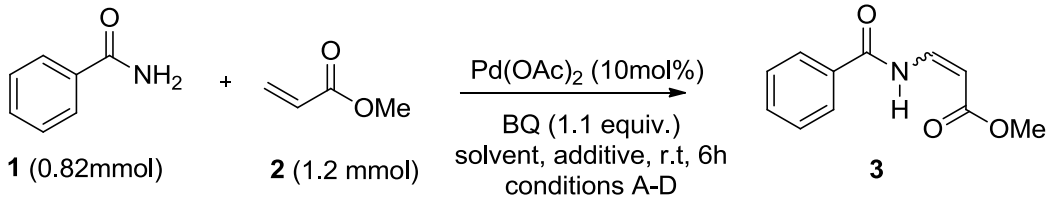
Although these achievements towards enamides synthesis via oxidative amidation reaction are promising, limited substrate scope, poor stereoselectivity and requirement of ambient reaction conditions often demand for new catalytic systems that can further improve the reaction efficiency and scope, thus making this approach more attractive. Herein, we reveal a highly efficient, copper-free, Pd-catalyzed protocol for the direct amidation of electron deficient olefins. This reaction proceeds at room temperature with wide substrate scope and results in some novel enamides with high *Z*-selectivity.

2.2 Results and Discussion

We initiated our study by conducting the $Pd(OAc)_2$ catalyzed oxidative amidation of methyl acrylate (**2**) with benzamide (**1**) under various reaction conditions (Table 1). We observed that solvent polarity had a significant effect on the efficiency and selectivity of the process. For instance, when reaction was carried out in the polar solvents like dimethyl sulfoxide, dimethyl formamide, tetrahydrofuran and so forth the starting material was not completely consume after 24 h and resulted in poor yield of the enamide **3** along with the formation of polymerized products (Table 1, entries 7−12). Additionally in polar solvents, the selectivity of the reaction lost with the formation more amount of *E*-isomer. In contrast, when the reaction was carried out in nonpolar solvent like toluene, the amidation reaction proceeded smoothly and gave 76% of *Z*-enamide **3** selectively (Table 1, entry 5). The presence of an acid is found to be very crucial.[7] The reaction proceeds well in the presence of acetic acid; however, the addition of 0.5−1.0 equiv of p-TsOH results in the best yield of **3**. Without acid the, reaction does not proceed even in the presence of an oxidant. Evidently, this is due to the in situ formation of a reactive palladium mono- or bistosylate species[8] from the $Pd(OAc)_2$ precatalyst which results in the increase of the electrophilicity of Pd(II) center

for faster metalation of methyl acrylate. Instead of taking TsOH as additives, when 10 mol % of $Pd(OTs)_2$ was taken directly in the amidation reaction, the yield of enamide **3** then reduced to 24%. Thus, excess of Brønsted acid is found to be beneficial to improve the efficiency of the catalytic process.

Table 1. Optimization reaction of benzamide with methyl acrylate.



1 (0.82mmol) **2** (1.2 mmol) **3**

Entry	Solvent	additive	condition	% yield (*Z:E*)
1	toluene	--	A	00
2	toluene	AcOH	A	38 (Z only)
3	toluene	p-TsOH (0.5 equiv)	A	66 (Z only)
4	toluene	p-TsOH (0.5 equiv)	B	60 (Z only)
5	**toluene**	**p-TsOH (0.5 equiv)**	**C**	**76 (Z only)**
6	toluene	p-TsOH (0.5 equiv)	D	55 (2:1)
7	1,4-dioxane	p-TsOH (0.5 equiv)	C	62 (2.5:1)
8	DCE	p-TsOH (0.5 equiv)	A	45 (3.3:1)
9	THF	p-TsOH (0.5 equiv)	A	40 (1:9)
10	DMF	p-TsOH (0.5 equiv)	A	32 (1:10)
11	DMSO	p-TsOH (0.5 equiv)	A	35 (1:13)
12	Toluene/H_2O (4:1)	p-TsOH (0.5 equiv)	A	40 (Z only)

Reaction Conditions A: benzamide (1 equiv.), olefin (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.1 equiv.), air.

B: benzamide (1 equiv.), olefin (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.1 equiv.), molecular sieves (4 A°), N_2 atmosphere.

C: benzamide (1 equiv.), olefin (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.1 equiv.), molecular sieves 4A°, air.

D: benzamide (1 equiv.), olefin (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.1 equiv.), $Cu(OAc)_2$ (10 mol %), air.

When the amidation reaction was conducted in toluene at room temperature using $Cu(OAc)_2$ as oxidant, a mixture of *E* and *Z*-enamides was obtained (Table 1, entry 6) and in turn this is in agreement with the observations of Liu and Hii.[6] In contrast, when benzoquinone (BQ) was used as oxidant in place of $Cu(OAc)_2$ only *Z*-enamide **3** was obtained. Moreover, examples on Cu(II)-mediated isomerization of amides have literature precedent.[9] For instance, Lectka and his co-workers[10] reported that presence of copper (II) ions substantially lowers the amide rotation barrier through co-ordination of the metal ion with the amide N (Scheme 6). As a result, amides often undergo isomerisation in the presence of Cu-catalyst. We may presume here that for the same reason mixture of *Z*-and *E*-enamdes are formed in the presence of $Cu(OAc)_2$. However, the exact mechanism of Cu-mediated isomerization of enamide is not clear at this stage.

Scheme 6

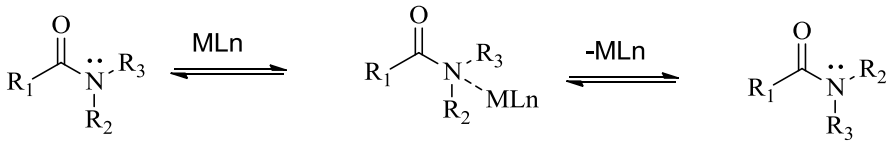
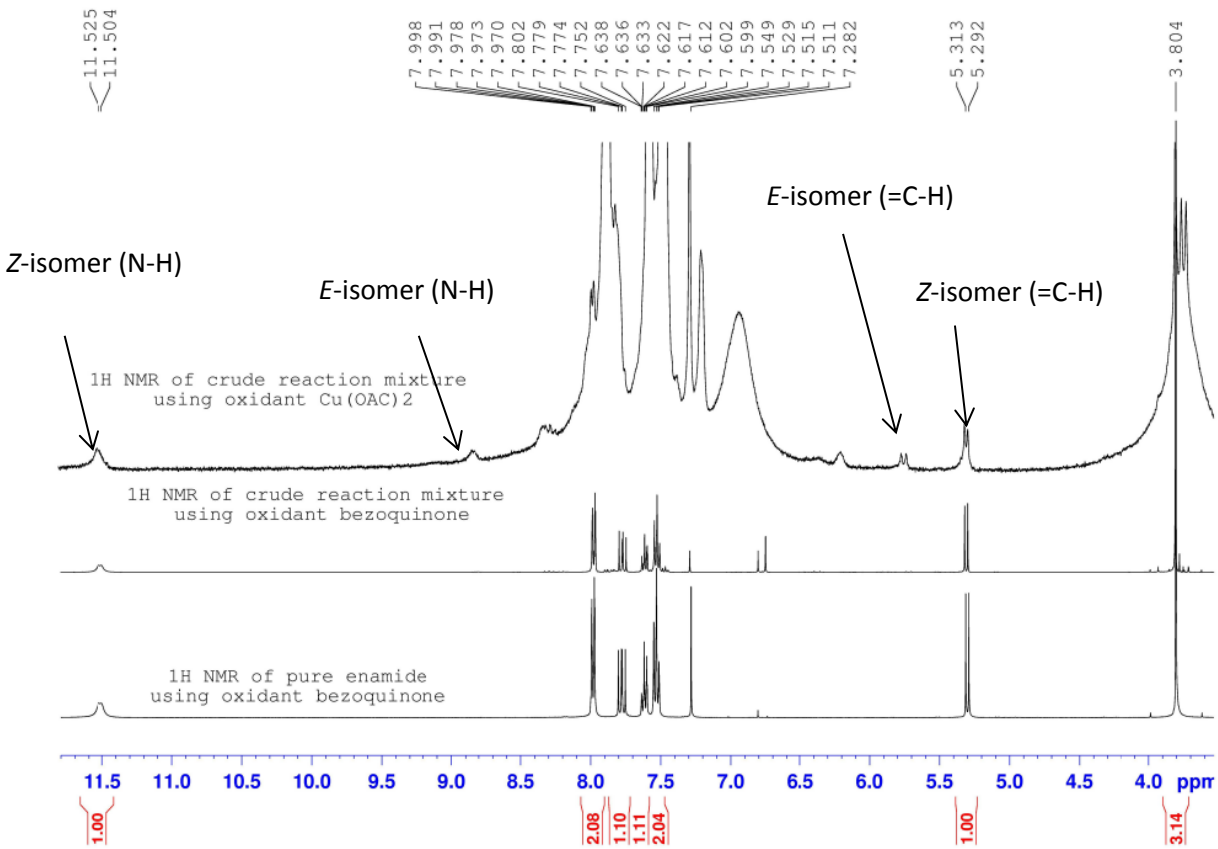
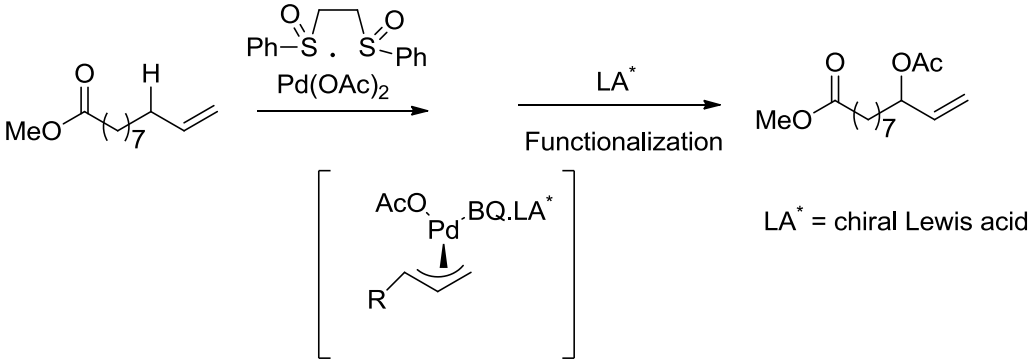


Figure 1.Comparison of NMR spectra using BQ and $Cu(OAc)_2$ as oxidant



Moreover, it is believed that BQ not only serves as an oxidant but also acts as a ligand to stabilize the different palladium species that resulted in the catalytic cycle.[11] Indeed, use of BQ as ligand for Pd species has literature precedent.[12] For example, Covell and White illustrated the formation of [(π-allyl) Pd(BQ)OAc] intermediate in the enantioselective allylic C−H oxidation of terminal olefins (Scheme 7).[13]

Scheme 7



Le Bras and co-workers also reported that BQ acts both as an oxidant and a ligand to stabilize Pd(0) by avoiding the formation of Pd black, thus facilitating the overall transformation.[14] Eventually it became apparent that water was detrimental to the reaction, and by employing molecular sieves with toluene as a solvent, enamide **3** was obtained in 76% yield after 6 hstirring at room temperature.

The yield of the reaction was almost unaffected even after prolonged stirring for 24 h. It may be noted that the increase in the catalyst loading from 10 to 20 to 50 mol % does not improve the product yield appreciably though the reason is unclear presently. It may be assumed that increased catalyst loading or prolonged stirring of the reaction mixture causes competitive polymerization. Use of 1 equiv of acetic anhydride instead of molecular sieves as a drying agent resulted in 60% yield of the enamide consistently, and this is in line with the observations of Loyd-Jones and Milburn for C−H activation.[8] Furthermore, an increase of reaction temperature (room temperature to 60 °C) has no accelerating effect on the reaction rate; rather, the yield of the product reduced because of the possible polymerization. When the product enamide **3** was heated with $Pd(OAc)_2$, BQ, p-TsOH in the presence of molecular sieves in toluene at 60 °C, complete decomposition takes place.

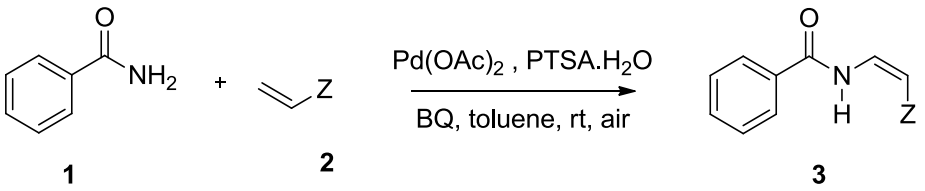
The use of excess amount of amide or olefin does not affect the product yield significantly. Another important observation in the oxidative amidation is that the reaction proceeds successfully in the presence of ambient air. In presence of N_2 atmosphere, the reaction becomes sluggish and results in 60% yield of enamide **3**. To ascertain this catalytic

process as a "copper-free" catalytic process,[15] chemical analysis of the $Pd(OAc)_2$ sample was performed using atomic absorption spectroscopy, and we did not find any trace of Cu even at parts per million (ppm) level.

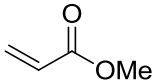
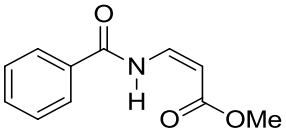
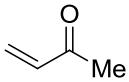
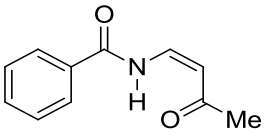
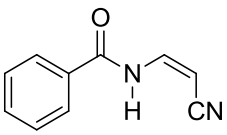
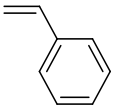
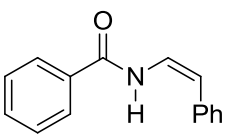
Substrate Scope

With these optimized conditions in hand, we explored the scope of the reaction with a variety of substituted alkenes. With the parent system 1 it was found that electron-deficient alkenes made the best coupling partners, and unactivated alkenes such as styrene and 4-vinylpyridine were inactive to give the corresponding enamide. Interestingly, under our reaction conditions the former coupling partners exclusively give the *Z*-enamides, and we did not found any trace of *E*-isomer in the crude reaction mixture from NMR study (Figure 2). Formation of *Z*-enamide is evident from the spectral data. For example, the appearance of doublets at δ 11.5 (for N − H) and 5.27 (vinylic proton) with coupling constant 8.8 Hz reveals the formation of *Z*-enamide.

Table 2



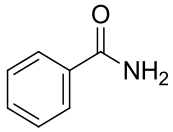
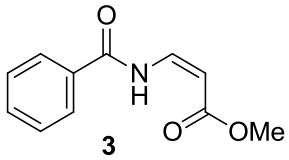
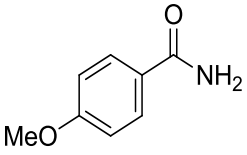
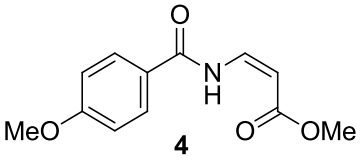
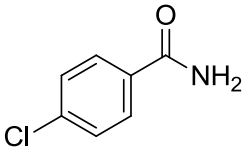
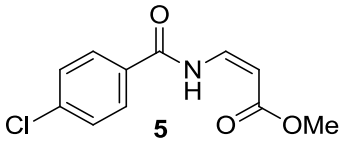
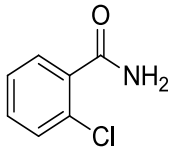
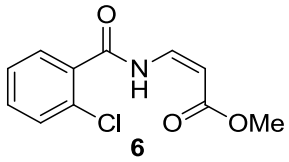
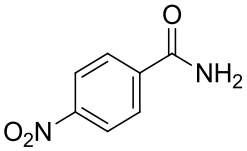
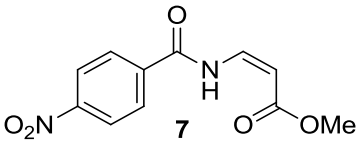
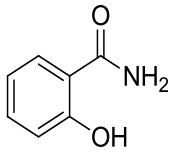
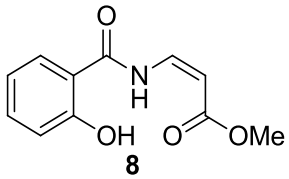
1 2 3

Entry	Substrate	Product	% Yield
1			76
2			45
3			15
4			<5

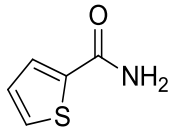
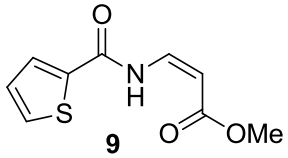
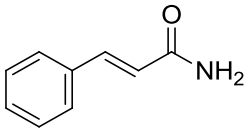
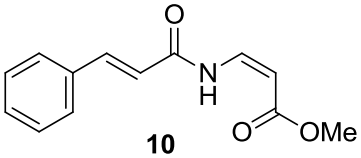
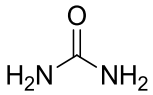
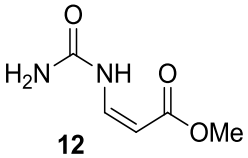
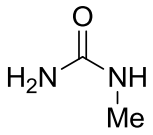
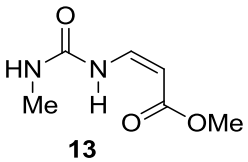
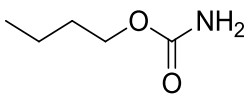
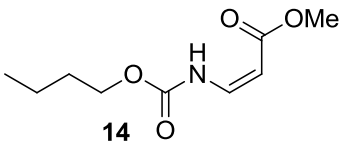
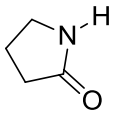
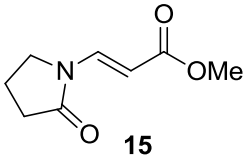
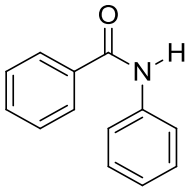
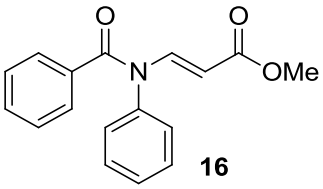
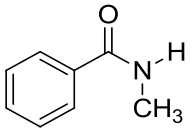
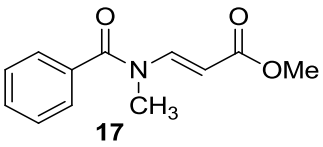
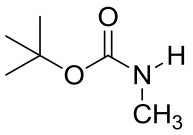
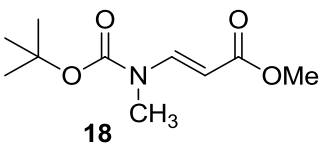
Reaction conditions: benzamide (1 equiv.), olefin (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.1 equiv.), *p*-TsOH (0.5 equiv).

Next we extended the scope of the oxidative amidation reaction using a range of amides with methyl acrylate (Table 3). It turned out that primary amides of alkyl and aryl adducts cross-couple with methyl acrylate and lead to the *Z*-enamides. This catalytic protocol was found to be tolerant to aryl ring substitutions, and in most cases moderate to good yields of enamides was obtained. As such, electron withdrawing substituents (i.e., $-NO_2$, Cl) that decrease the nucleophilicityof amide still couple with methyl acrylate and lead to the *Z*-enamides in good yield without affecting the selectivity (Table 3, entries: 3−5).

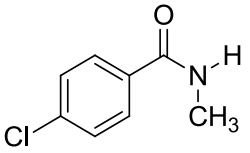
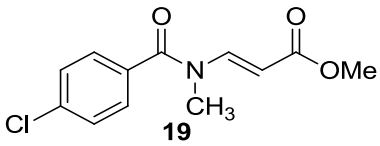
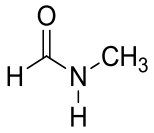
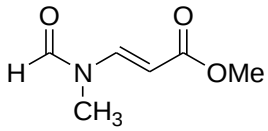
Table 3. Substrate Scope

Entry	Substrate	Product	method	Time(h)	Yield (%)
1		 **3**	A	6	76
2		 **4**	A	12	65
3		 **5**	A	28	40
4		 **6**	A	10	64
5		 **7**	B	10	48
6		 **8**	A	12	57(9:1)

Continued…

7		 **9**	A	10	63
8		 **10**	B	12	55
10		 **12**	B	10	45
11		 **13**	B	12	40
12		 **14**	A	12	64
13		 **15**	A	12	65
14		 **16**	A	36	45
15		 **17**	A	36	35
16		 **18**	A	10	56

Continued…

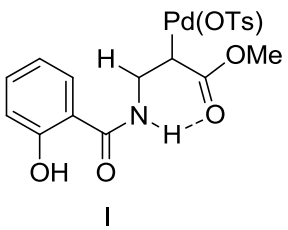
17		 **19**	A	24	40
18		 **20**	A	12	63

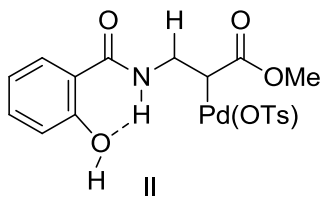
Reaction conditions: amide (1 equiv.), olefin (1.5 equiv.), $Pd(OAc)_2$ (10 mol %), BQ (1.1 equiv.), *p*-TsOH (0.5 equiv)

Urea and carbamates also underwent cross-coupling with methyl acrylate and furnished some novel enamides in modest yield. Reactions of ureas resulted in *Z*-enamides, with functionalization of only one of the nitrogen atoms (Table 3, entries 10 and 11), even in the presence of excess methyl acrylate. When cyclic amide such as pyrrolidinone was subjected to cross-coupling with methyl acrylate, only the thermodynamically favourable *E*-enamide (J = 14 Hz) was obtained (Table 3, entry 13). This again substantiates the significance of intramolecular hydrogen bonding in enamide synthesis. Finally, the scope of our protocol has been extended to the sterically hindered enamides (Table 3, entries 14−18). In the earlier system reported by Liu and Hii,[6] the reaction of acyclic sterically more hindered secondary amides, such as *N*-methyl acetamide, *N*-methyl benzamide with butyl acrylate was found to be ineffective (<5%) despite their higher nucleophilicity. Benzanilide undergoes ortho C−H bond activation under similar reaction conditions.[11]

Moreover, the formation of tertiary enamides from sterically hindered secondary amides has less literature precedent.[16] To our pleasure, the developed catalytic system was found to be tolerant to such steric hindrance offered by the secondary amides such as benzanilides and carbamates and furnishes tertiary enamides in good yield even at room temperature. In contrast, when salicylamide reacts with methyl acrylate (Table 3, entry 6), it results in the mixture of *E/Z*- isomers.

Scheme 8: Hypothetical σ-Alkylpalladium Tosylate Complex.


I

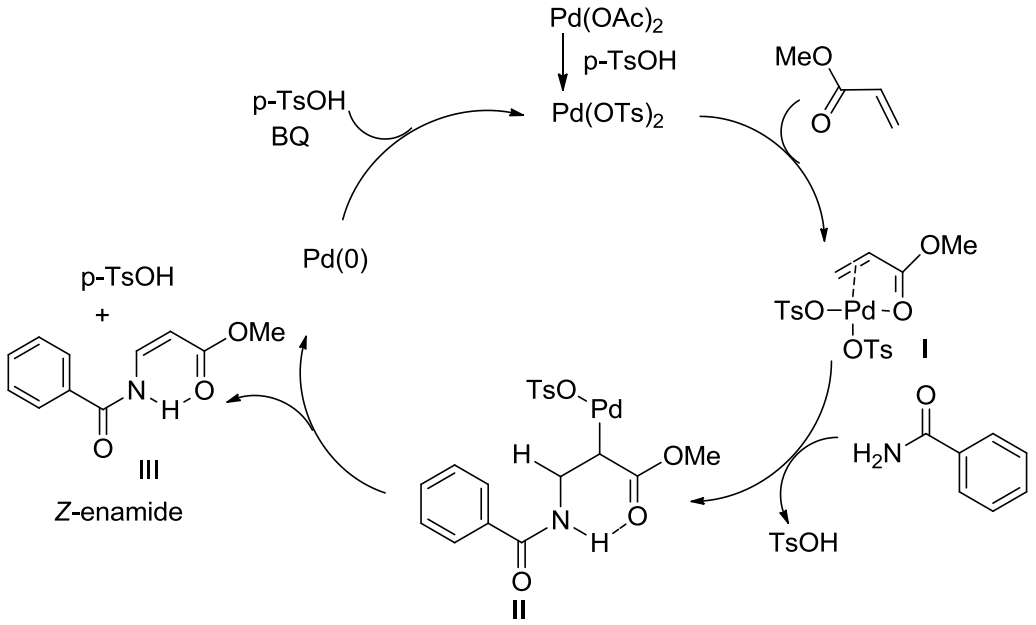

II

This may be due to the favorable intramolecular hydrogen bonding in salicylamide (-HO•••H−N), which inhibits theextent of hydrogen bonding between N−H and C-O group of methyl acrylate.

Plausible mechanism

The possible mechanism for the oxidative coupling of benzamide and methyl acrylate to explain the *Z*-selectivity is depicted in Scheme 9. Evidently, the palladium mono- or bistosylate generated from $Pd(OAc)_2$ undergoes oxidative addition with methyl acrylate to give palladium-olefine complex (I). Nucleophilic attack of the amide to the complex **I** leads to the hydrogen bonded σ-alkylpalladium tosylate complex**II**. Subsequent β-hydride elimination from the hydrogen bonded complex **II**, results in the *Z*-enamide exclusively.

Scheme 9: Catalytic cycle for *Z*-enamide synthesis



2.3 Conclusions

We have demonstrated an improved catalytic protocol for the oxidative amidation of olefins in the presence of ambient air. A wide range of amides and olefins were found to be reactive forthe generation of enamides at room temperature. The reactions were found to be acid catalyzed and p-TsOH gave the best result in enamide synthesis. The reactions were conducted at room temperature in the presence of ambient air. This protocol has wide substrate scope allowing alkyl, aryl, substituted arylamides, urea, and its derivatives to react with methyl acrylate. The high stereoselectivity is mainly attributed to the favorable β-

hydride elimination from the hydrogen bonded σ-alkylpalladium tosylate intermediate. This protocol is found to be suitable for the cross coupling of sterically hindered secondary amides with electron deficient olefins leading to tertiary enamides in good yield. We strongly believe that the distinct simplicity of this catalytic system would render its wide usage useful in organic synthesis.

2.4 Experimental

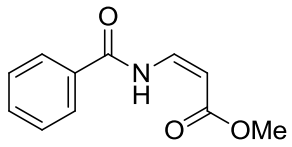
General procedure for enamide synthesis:

Method A: A mixture of amide (100 mg), $Pd(OAc)_2$ (10 mol%), benzoquinone (1.1 equiv.), PTSA.H_2O (0.5 eq.), in toluene (4 ml) was stirred for 5 minutes under open air at room temperature. To this reaction mixture olefin (1.5 equiv.) was added drop wise. The resulting blood red reaction mixture was then stirred for the appropriate time at room temperature under open air. After the completion of the reaction (as monitored by TLC) dichloromethane followed by water was added. The layers were separated. The aqueous layer was extracted with dichloromethane and the combined organic layer was washed with water (twice). The dichloromethane layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The crude residue was subjected to column chromatography on silica gel with petroleum ether and ethyl acetate as eluent to give the pure enamide.

Method B: Instead of toluene, 1,4-dioxane was taken and remaining procedure is exactly similar to Method **A**.

Synthesis and analytical data of enamides

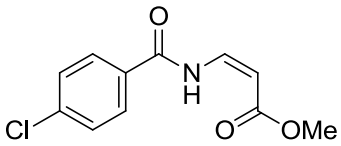
(*Z*)-Methyl 3-(benzamido)acrylate (3)



Following the general procedure (Method A) benzamide (100 mg, 0.825 mmol), benzoquinone (98 mg, 0.907 mmol), PTSA.H_2O (71 mg, 0.412 mmol), molecular sieves (70 mg, 4Å) and $Pd(OAc)_2$ (18 mg, 0.08 mmol) was stirred in toluene for one minute. To the resulting mixture methyl acrylate (0.11 mL, 1.237 mmol) was added under open air and stirring was continued for 6 h. The crude mixture was then purified by silica gel chromatography (Petroleum ether: ethyl acetate 95: 5) and gave 129 mg (76%) of the desired product **3** as a white crystalline solid.MP: 73-74 ^{0}C IR (KBr): 3323, 2952, 1685, 1636, 1581,

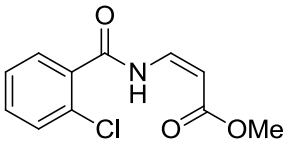
1508, 1478, cm^{-1}. ^{1}H NMR (400 MHz, CDCl3): δ 11.51 (d, 1H, *J* = 8.8 Hz), 8.00-7.94 (m, 2H), 7.77 (dd, 1H, J_1=11.2 Hz, J_2 = 8.8 Hz), 7.64-7.56 (m, 1H), 7.55-7.48 (m, 2H), 5.29 (d, 1H, *J* = 8.8 Hz). 3.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 170.0, 164.5, 138.9, 132.9, 132.1, 128.9, 127.7, 96.6, 51.4. Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; O, 23.39; Found: C, 64.40; H, 5.38; N, 6.72; O, 23.59 MS (ES+) m/z (relative intensity) 206 ($[M+H]^+$, 100%).

(*Z*)-Methyl 3-(4-chlorobenzamido)acrylate (4)



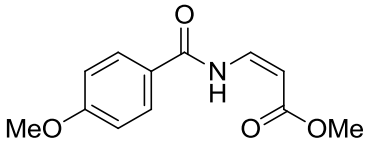
Following method **A**, 4-chlorobenzamide (100 mg, 0.65 mmol) gave 66 mg (40%) of *Z*-enamide as a white crystalline solid. MP: 107-110 °C IR (KBr): 3289, 2922, 1703, 1674, 1642, 1593, 1515, 1483 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3): δ 11.52 (d, 1H, *J* = 9.6 Hz), 7.96-7.88 (m, 2H), 7.74 (dd, 1H, J_1=11.2 Hz, J_2 = 8.8 Hz), 7.52-7.48 (m, 2H), 5.31 (d, 1H, J = 8.8 Hz), 3.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 170.1, 163.5, 139.4, 138.8, 130.5, 129.2, 129.1, 97.1, 51.5. Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; Cl, 14.79; N, 5.84; O, 20.03; Found: C, 55.23; H, 4.32; Cl, 14.69; N, 5.95; O, 20.23 MS (ES-API) m/z (relative intensity) 238 ($[M-H]^+$, 100%).

(*Z*)-Methyl 3-(2-chlorobenzamido)acrylate (5)



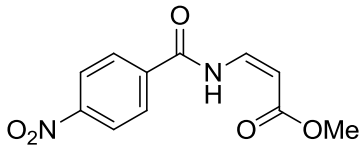
Following method **A**, 2-chlorobenzamide (100 mg, 0.65 mmol) gave 101 mg (64%) of corresponding *Z*-enamide as a white crystalline solid. MP: 80-82°C ^{1}H NMR (400 MHz, CDCl3): δ 11.16 (d, 1H, *J* = 8.8 Hz), 7.80-7.68 (m, 2H), 7.51-7.34 (m, 3H), 5.31 (d, 1H, *J* = 8.8 Hz), 3.76 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 169.2, 164.4, 137.7, 133.1, 132.4, 131.5, 130.8, 130.6, 127.2, 97.6, 51.4. Anal. Calcd. for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; Cl, 14.79; N, 5.84; O, 20.03; Found: C, 55.20; H, 4.35; Cl, 14.99; N, 5.98; O, 20.18

(*Z*)-Methyl 3-(4-methoxybenzamido)acrylate (6)



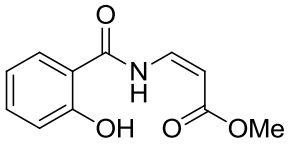
Following method**A**, 4-methoxybenzamide (100mg, 0.671 mmol) gave 101 mg (65%) of corresponding *Z*-enamide as a white crystalline solid. MP: 97-99 °C. IR (KBr): 3331, 2954, 2922, 1692, 1641, 1607, 1485, 1431, 1382 cm^{-1}.^{1}H NMR (400 MHz, CDCl3): δ 11.45 (d, 1H, *J* = 10 Hz), 7.95 (d, 2H, *J* = 8.8 Hz), 7.76 (dd, 1H, J_1 = 11.2 Hz, J_2 = 8.8 Hz), 7.00 (d, 2H, *J* = 8.8 Hz), 5.26 (d, 1H, *J* = 8.8 Hz), 3.90 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 170.1, 163.9, 163.3, 139.3, 129.8, 124.3, 114.1, 95.9, 55.5, 51.3. MS (ES+) m/z (relative intensity) 236 ($[M+H]^+$, 100%).

(*Z*)-Methyl 3-(4-nitrobenzamido)acrylate (7)



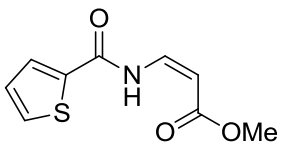
Following method **B**, 4-nitrobenzamide (100 mg, 0.598 mmol) gave 72 mg (48%) of the desired product **7** as a white crystalline solid. MP: 131-133 °C. IR (KBr): 3284, 2954, 1711, 1674, 1626, 1601, 1520, 1434 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3): δ 11.67 (d, 1H, *J* = 9.2 Hz), 8.37 (d, 2H, *J* = 11.2 Hz), 8.14 (d, 2H, *J* = 11.2 Hz), 7.74 (dd, 1H, J_1 = 10.8 Hz, J_2 = 8.8 Hz), 5.38 (d, 1H, J = 8.8 Hz), 3.81 (s, 3H).^{13}C NMR (100 MHz, CDCl3): δ 170.0, 162.5, 150.3, 138.3, 137.6, 128.8, 124.1, 98.3, 51.6. MS (ES-TOF) m/z (relative intensity) 273 ($[M+Na]^+$, 100%).

(*Z*)-Methyl 3-(2-hydroxybenzamido)acrylate (8)



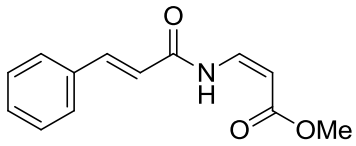
Following method **A**, salicylamide (100 mg, 0.73 mmol), gave 93 mg (57%) of the desired product **4** as a white crystalline solid. IR (KBr): 3311, 2956, 1683, 1660, 1660, 1630, 1602, 1517, 1436, 1388, 1359 cm-1. ^{1}H NMR (400 MHz, CDCl3): δ 11.82 (s, 1H), 11.72 (d, 1H, *J* = 9.2 Hz), 7.78-7.68 (m, 1H), 7.62 (dd, 1H, J_1 = 10.4 Hz, J_2 = 8.8 Hz), 7.54-7.46 (m, 1H), 7.08-7.02 (m, 1H), 7.00-6.94 (m, 1H), 5.36 (d, 1H, *J* = 8.8 Hz), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 167.8, 162.6, 137.7, 135.7, 126.3,119.4, 118.8, 113.0, 97.7, 51.6. MS (ES+) m/z (relative intensity) 222 ($[M+H]^+$, 100%).

(*Z*)-Methyl 3-(thiophene-2-carboxamido)acrylate (9)



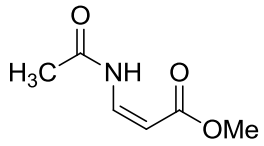
Following method **A**, thiophene 2-carboxamide (100 mg, 0.787 mmol) reacts with methyl acrylate and gave 100 mg (60 %) of the desired product **9** as a white crystalline solid. MP: 110-112°C IR (KBr): 3333, 3076, 2949, 1670, 1628, 1522, 1474, 1432 cm-1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.37 (d, 1H, *J* = 8.8 Hz), 7.76-7.73 (m, 1H), 7.69 (dd, 1H, J_1 = 10.8 Hz, J_2 = 8.8 Hz), 7.66-7.64 (m, 1H), 7.20-7.14 (m, 1H), 5.27 (d, 1H, *J* = 8.8 Hz), 3.79 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 169.9, 159.2, 138.5, 137.2, 132.6, 130.0, 128.1, 96.5, 51.4. Anal. Calcd. for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63; O, 22.72; S, 15.18; Found: C, 51.28; H, 4.23; N, 6.89; O, 22.90; S, 15.22 MS (ES) m/z (relative intensity) 212 ($[M+H]^+$, 100%).

(2*Z*)-Methyl 3-(cinnamamido)acrylate (10)



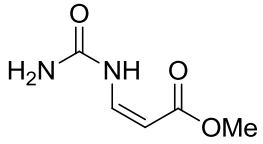
Following method **B**, cinnamide (100 mg, 0.680 mmol) reacts with methyl acrylate in 1,4-dioxane to give 85 mg (55 %) of the enamide as a colourless oil. IR (neat): 3328, 2949, 1686, 1629, 1433, 1381 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (d, 1H, *J* = 10.4 Hz), 7.79 (d, 1H, *J* = 15.6 Hz), 7.67 (dd,1H, J_1 = 11.2 Hz, J_2 = 9.2 Hz), 7.44-7.31 (m, 5H), 6.53 (d, 1H, *J* = 15.6 Hz), 5.22 (d, 1H, *J* = 9.2 Hz), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 163.5, 144.6, 138.6, 134.1, 130.6, 128.9, 128.2, 119.1, 96.3, 51.3. MS (ES) m/z (relative intensity) 232 ($[M+H]^+$, 100%).

(*Z*)-Methyl 3-acetamidoacrylate (11)



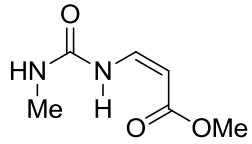
Following method **B**, acetamide (100 mg, 1.69 mmol) reacts with methyl acrylate in 1,4-dioxane and gave 109 mg (46 %) of the desired product **11** as a yellow oil. IR (neat): 3319, 2955, 1693, 1631, 1535, 1436 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (br s, 1H), 7.49 (dd, 1H, J_1 = 11.6 Hz, J_2 = 8.8 Hz), 5.14 (d, 1H, *J* = 9.2 Hz), 3.73 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 168.3, 138.1, 95.8, 51.3, 23.6. Anal. Calcd. for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79; O, 33.53; Found: 50.26; H, 6.48; N, 9.95; O, 33.59 MS (ES) m/z (relative intensity) 144 ($[M+H]^+$, 100%).

(*Z*)-Methyl 3-ureidoacrylate (12)



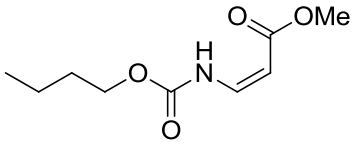
Following method **B**, urea (100 mg, 1.66 mmol) reacts with methyl acrylate in 1,4-dioxane to furnish 83 mg (35 %) of the desired product as a gummy semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (d, 1H, J = 10.8 Hz), 7.45 (dd, 1H, J_1 = 11.6 Hz, J_2 = 8.8 Hz), 5.47 (brs, 2H), 5.03 (d, 1H, J = 8.8 Hz), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 154.3, 140.8, 92.6, 51.1. MS (ES) m/z (relative intensity) 145 ($[M+H]^+$, 100%).

(*Z*)-methyl 3-(3-methylureido)acrylate (13)



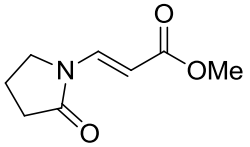
Following method **B**, *N*-methyl urea (100 mg, 1.35 mmol reacts with methyl acrylate in 1,4-dioxane to give 85 mg (40 %) of the desired product as a gummy liquid. ^{1}H NMR (400 MHz, CDCl3): δ 9.89 (br s, 1H), 7.52 (dd, 1H, J_1 = 11.6 Hz, J_2 = 8.8 Hz), 5.47 (br s, 1H), 4.98 (d, 1H, J = 8 Hz), 3.70 (s, 3H), 2.89 (d, 3H, J = 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 154.2, 141.4, 91.1, 51.0, 27.1.

Butyl (*Z*)-2-(methoxycarbonyl)vinylcarbamate (14)



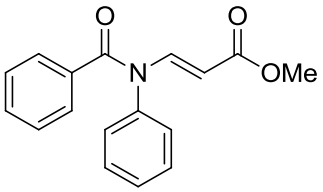
Following method **A**, n-butyl carbamate (100 mg, 0.85 mmol), reacts with methyl acrylate to furnish 113 mg (64 %) of the desired product as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (brs, 1H), 7.29 (dd, 1H, J_1=J_2 = 8.8 Hz), 5.05 (d, 1H, J = 8.8 Hz), 4.18 (t, 2H, J = 6.4 Hz), 3.72 (s, 3H), 1.72-1.55 (m, 2H), 1.52-1.29 (m, 2H), 0.89 (t, 3H, 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 153.6, 140.2, 94.2, 66.1, 51.1, 30.7, 18.9, 13.6. MS (ES) m/z (relative intensity) 202 ($[M+H]^+$, 100%).

(*E*)-Methyl 3-(2-oxopyrrolidin-1-yl)acrylate (15)



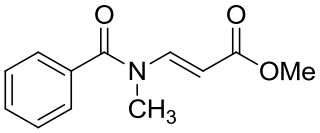
Following method **A**, 2-pyrrolidone (100 mg, 1.17 mmol) coupled with methyl acrylate in 1,4 dioxane at room temperature and gave 135 mg (65 %) of *E*-enamideas a white crystalline solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, 1H, *J* = 14.4 Hz), 5.22 (d, 1H, *J* = 14 Hz), 3.75 (s, 3H), 3.57 (t, 2H, *J* = 7.2 Hz), 2.57 (t, 2H,*J* = 8 Hz), 2.24-2.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 167.6, 137.4, 100.2, 51.4, 44.9, 30.9, 17.4. Anal. Calcd. for $C_8H_9NO_3$: C, 56.80; H, 6.55; N, 8.28; O, 28.37; Found: C, 56.66; H, 6.48; N, 8.55; O, 28.60. MS (ES) m/z (relative intensity) 170 ($[M+H]^+$, 100%).

(*E*)-Methyl 3-(N-phenylbenzamido)acrylate (16)



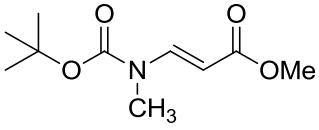
Following method **B**, *N*-phenylbenzamide (100 mg, 0.507 mmol) reacts with methyl acrylate to give 69 mg (49 %) of the desired *Z*-enamide as a white crystalline solid. MP: 145-146 °C IR (KBr): 3273, 2950, 1714, 1646, 1600, 1578, 1511, 1478 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.84 (m, 5H), 7.65-7.42 (m, 5H), 7.35-7.24 (m, 1H), 6.46 (d, 1H, *J* = 15.6 Hz), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 166.1, 139.4, 135.8, 134.2, 132.2, 130.9, 128.9, 127.9, 127.3, 127.2, 126.1, 125.2, 120.6, 51.9. Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; O, 17.06; Found: C, 72.88; H, 5.20; N, 4.78; O, 17.32. MS (ES) m/z (relative intensity) 282 ($[M+H]^+$, 100%).

(*E*)-Methyl 3-(N-methylbenzamido)acrylate (17)



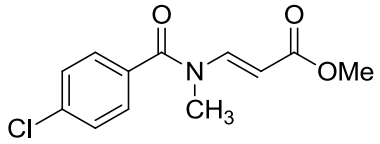
Following method **A**, desired enamide was obtained in 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, 1H, *J* = 14 Hz), 7.60-7.45 (m, 6H), 5.37 (d, 1H, J = 14 Hz), 3.71 (s, 3H), 3.30 (s, 3H). MS (ES) m/z (relative intensity) 220 ($[M+H]^+$, 100%).

Tert-butyl (*E*)-2-(methoxycarbonyl)vinylmethylcarbamate(18)



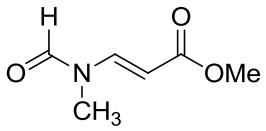
Following method A, tertiary butyl methylcarbamate (100 mg, 0.76 mmol), reacts with methyl acrylate in toluene to furnish 98 mg (60 %) of the desired product as a colourless oil. IR (neat): 2977, 2949, 1721, 1628, 1369 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, *J*= 14 Hz), 5.11 (d, 1H, *J* = 14 Hz), 3.72 (s, 3H), 3.05 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (s), 152.0, 143.6, 96.8, 83.1, 51.2, 31.0, 28.0. MS (ES) m/z (relative intensity) 216 ($[M+H]^+$, 100%).

(*E*)-Methyl 3-(4-chloro-N-methylbenzamido)acrylate (19)



Following method **A**, compound 19 was prepared as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H, *J* = 13.6 Hz), 7.51-7.45 (m, 4H), 5.38 (d, 1H, *J* = 14 Hz), 3.72 (s, 3H), 3.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 167.4, 144.2, 137.8, 131.8, 129.8, 129.1, 99.3, 51.4, 31.4.

(*E*)-Methyl 3-(N-methylformamido)acrylate (20)



Following method **A**, *N*-methylformamide (100 mg, 1.69 mmol) couples with methyl acrylate and furnished 152 mg (63%) of the desired compound as a white crystalline solid. IR (KBr): 3331, 2954, 2922, 1692, 1641, 1607, 1485 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.82 (d, 1H, *J* = 13.6 Hz), 5.44 (d, *J* = 13.6 Hz), 3.77 (s, 3H), 3.09(s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 163.1, 143.6, 99.5, 51.6, 27.7. MS (ES) m/z (relative intensity) 144 ($[M+H]^+$, 100%).

2.5 References

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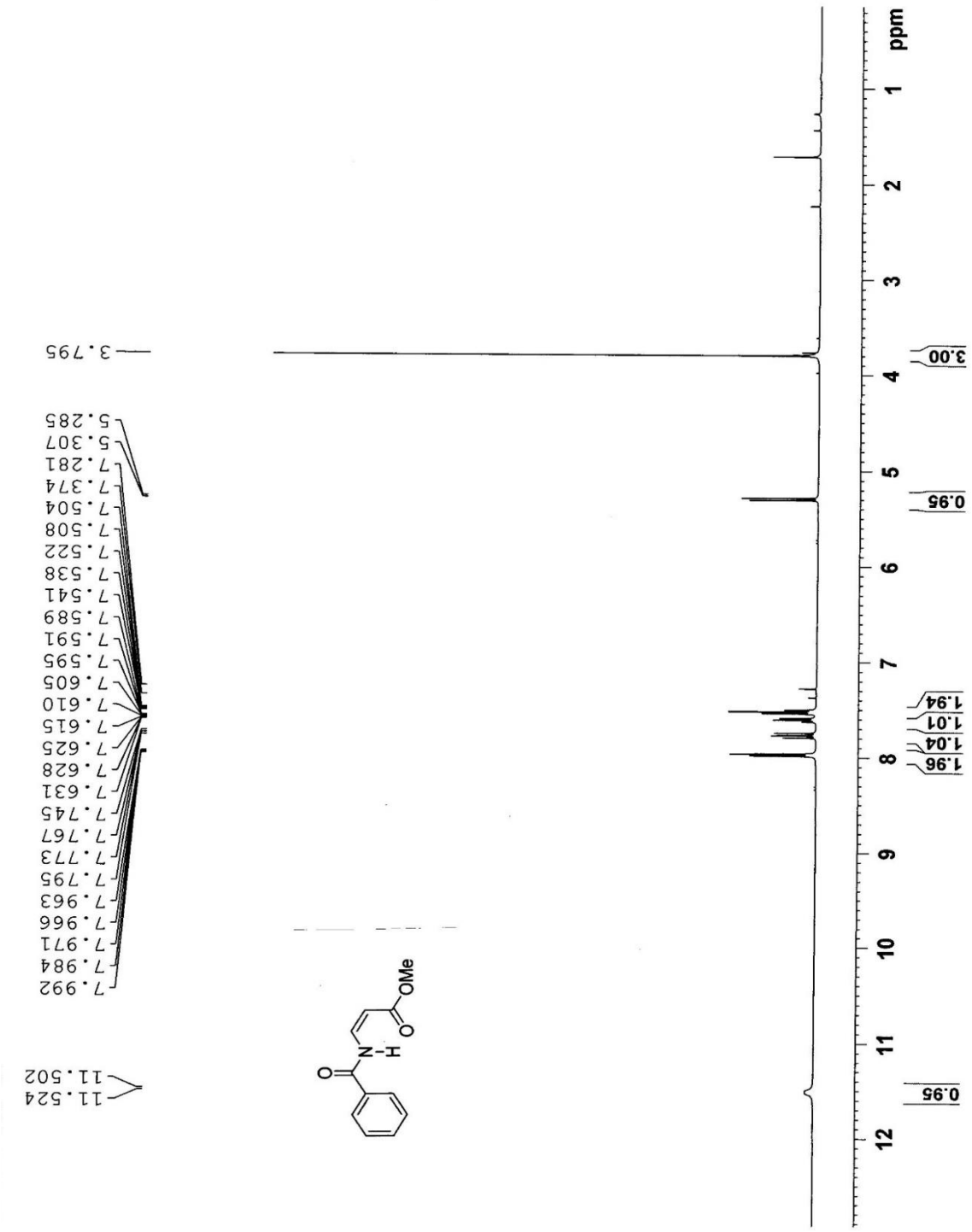
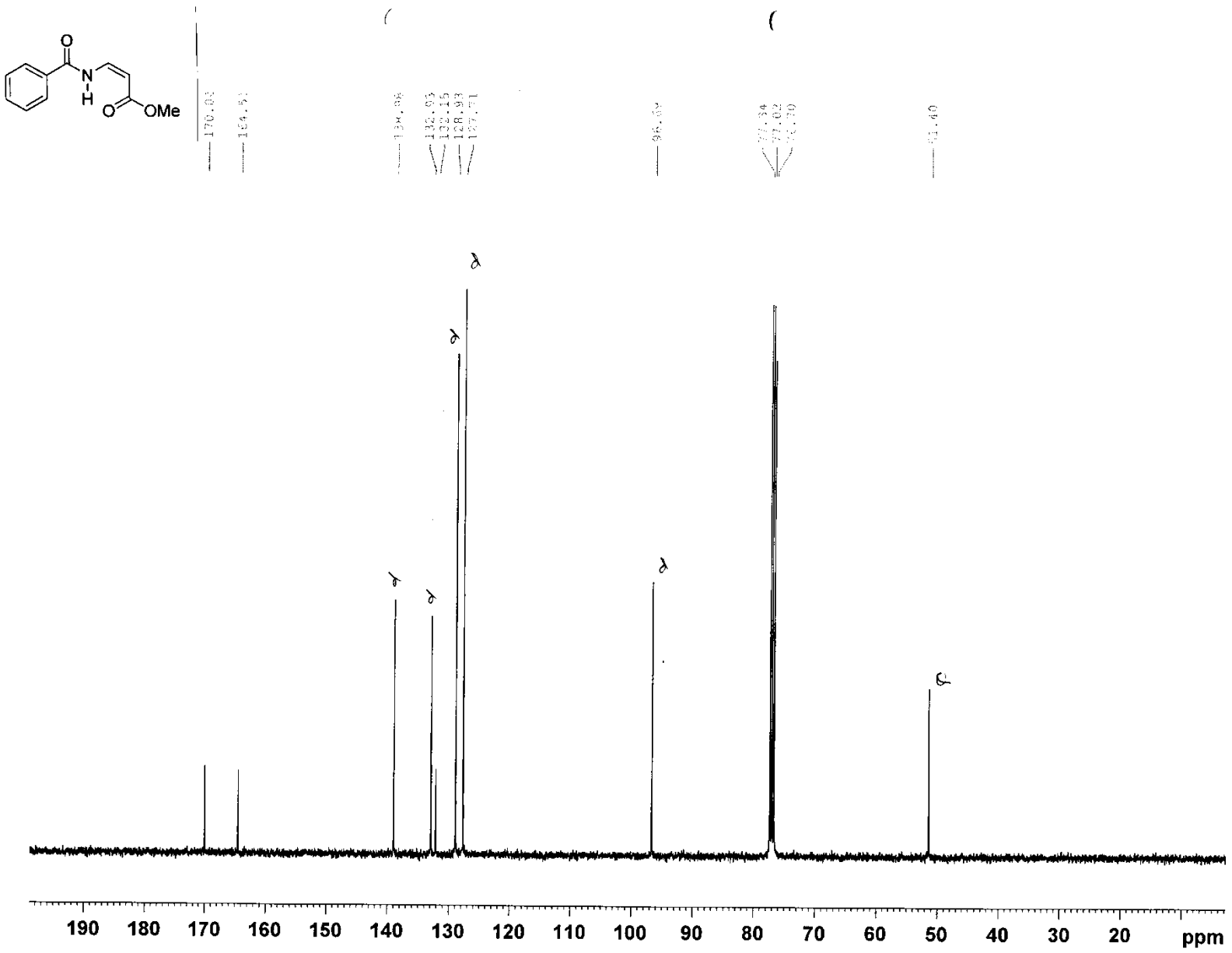
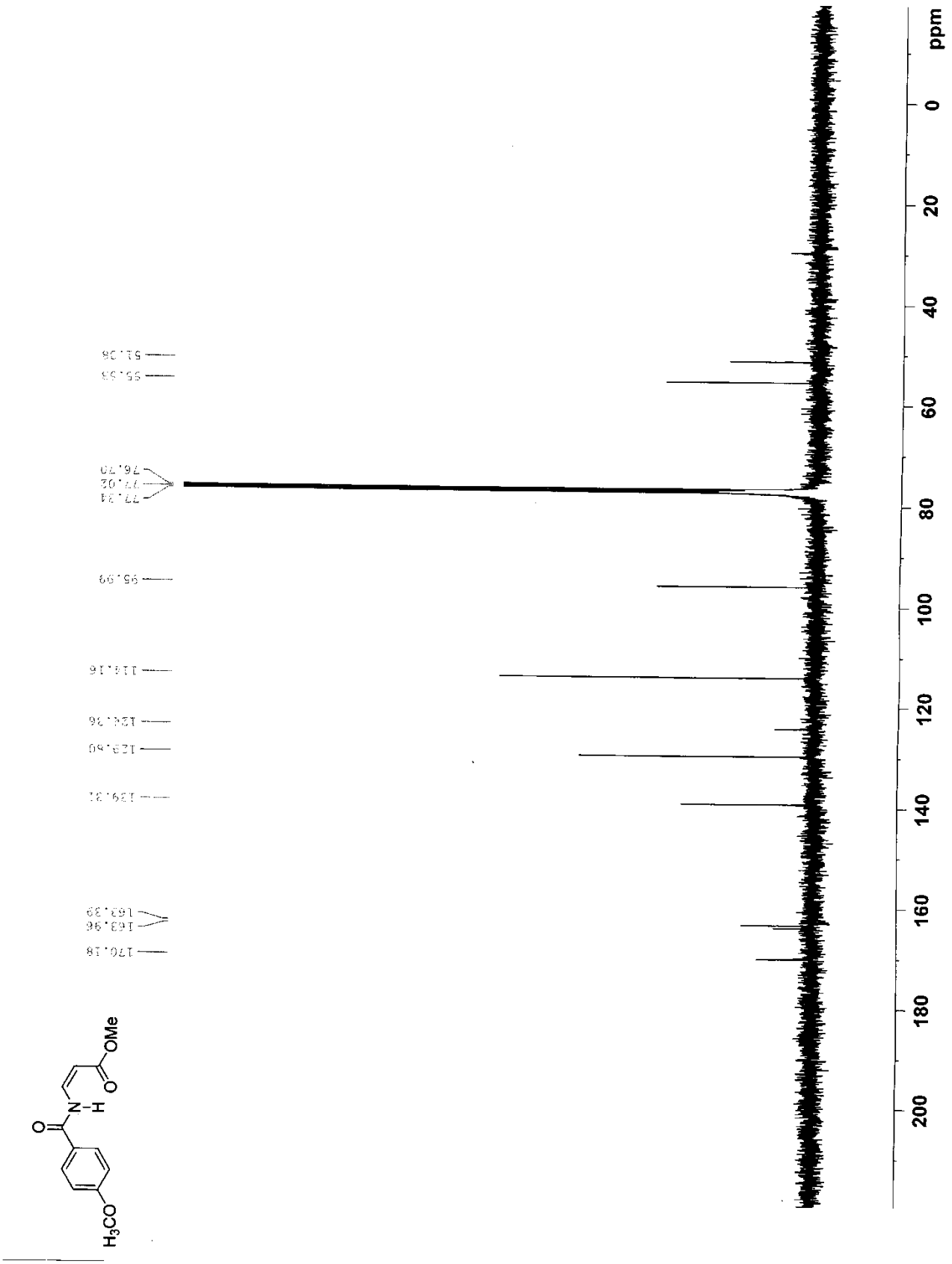
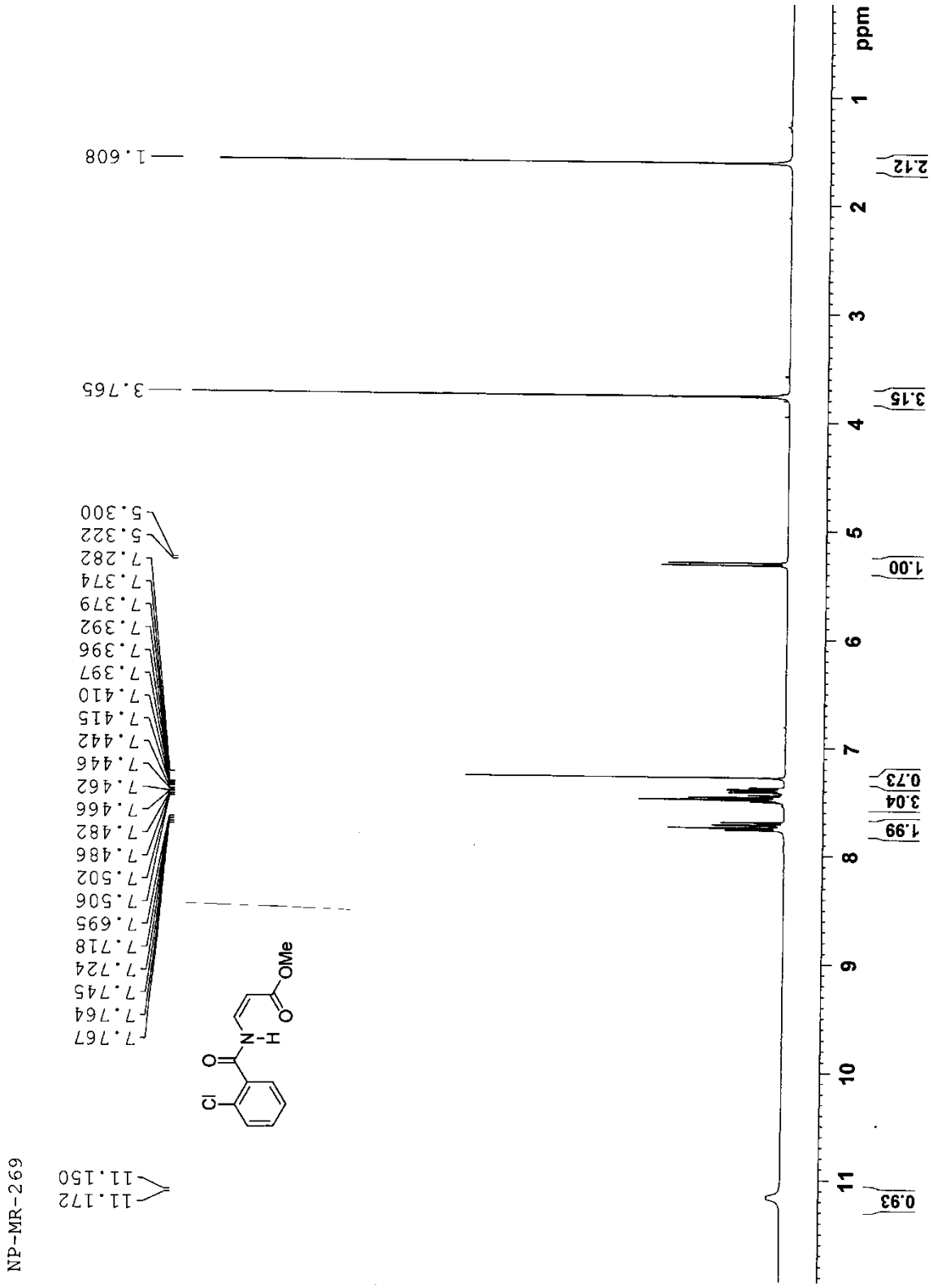
2.6 Selected NMR spectra




O
N
H
O
OMe
170.03
154.51
138.86
132.93
132.15
128.93
127.71
96.69
77.34
77.02
76.70
51.40
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

NP-MR-291
11.466
11.441
7.961
7.943
7.939
7.793
7.771
7.765
7.743
7.282
7.014
6.992
5.277
5.255
3.900
3.798
1.623
OMe
O
N
H
O
H3CO
ppm
1.02
2.20
1.25
2.17
1.00
3.33
3.67


51.36
55.55
76.79
77.02
77.34
95.89
116.16
124.36
129.60
139.31
162.39
163.96
170.18
O
N-H
O
OMe
O
H3CO
ppm
0
20
40
60
80
100
120
140
160
180
200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11.150
7.767
7.764
7.745
7.724
7.718
7.695
7.506
7.502
7.486
7.482
7.466
7.462
7.446
7.442
7.415
7.410
7.397
7.396
7.392
7.379
7.374
7.282
5.322
5.300
3.765
1.608
OMe
N-H
O
Cl
ppm
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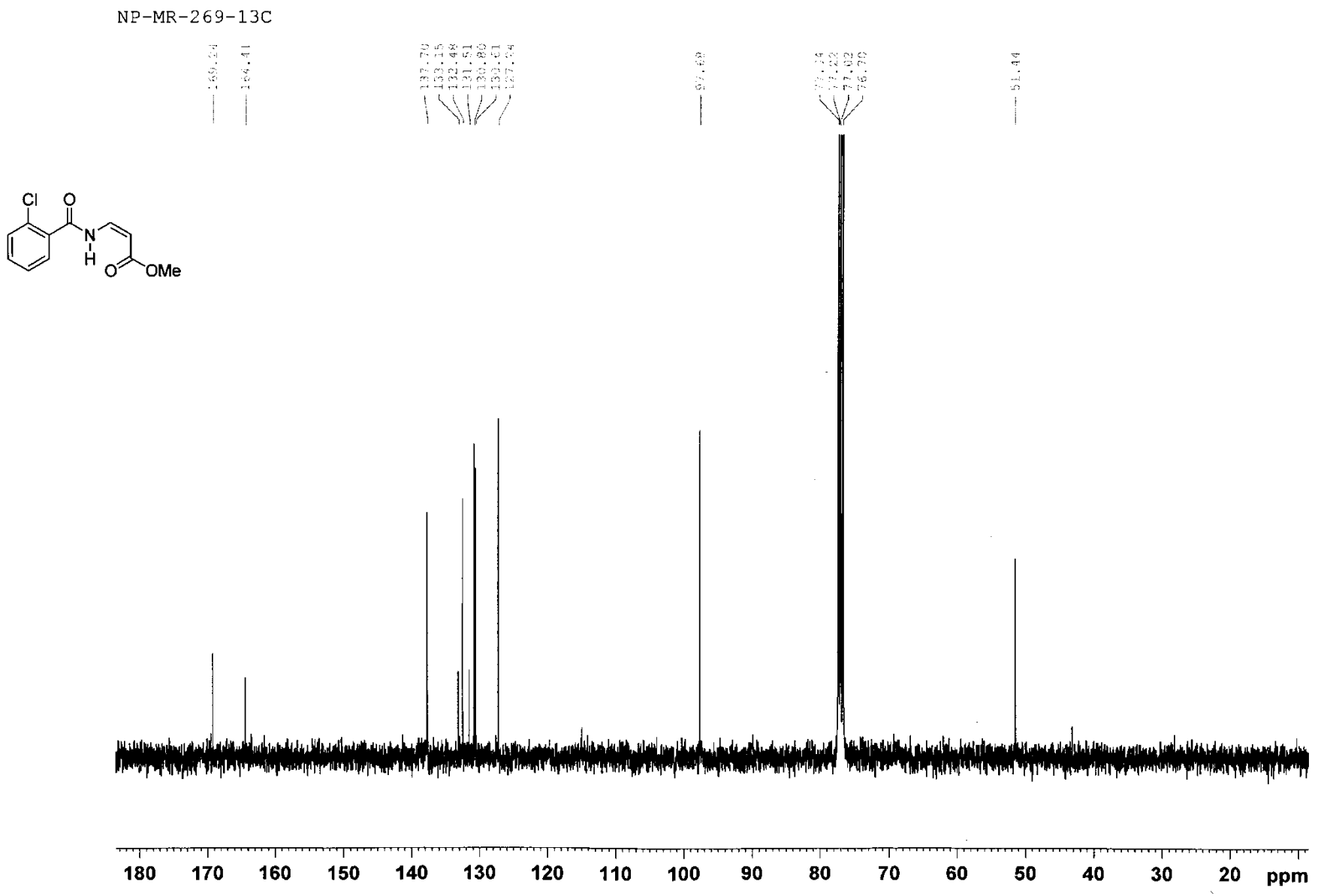
3.15
1.00
0.73
3.04
1.99


NP-MR-269-13C
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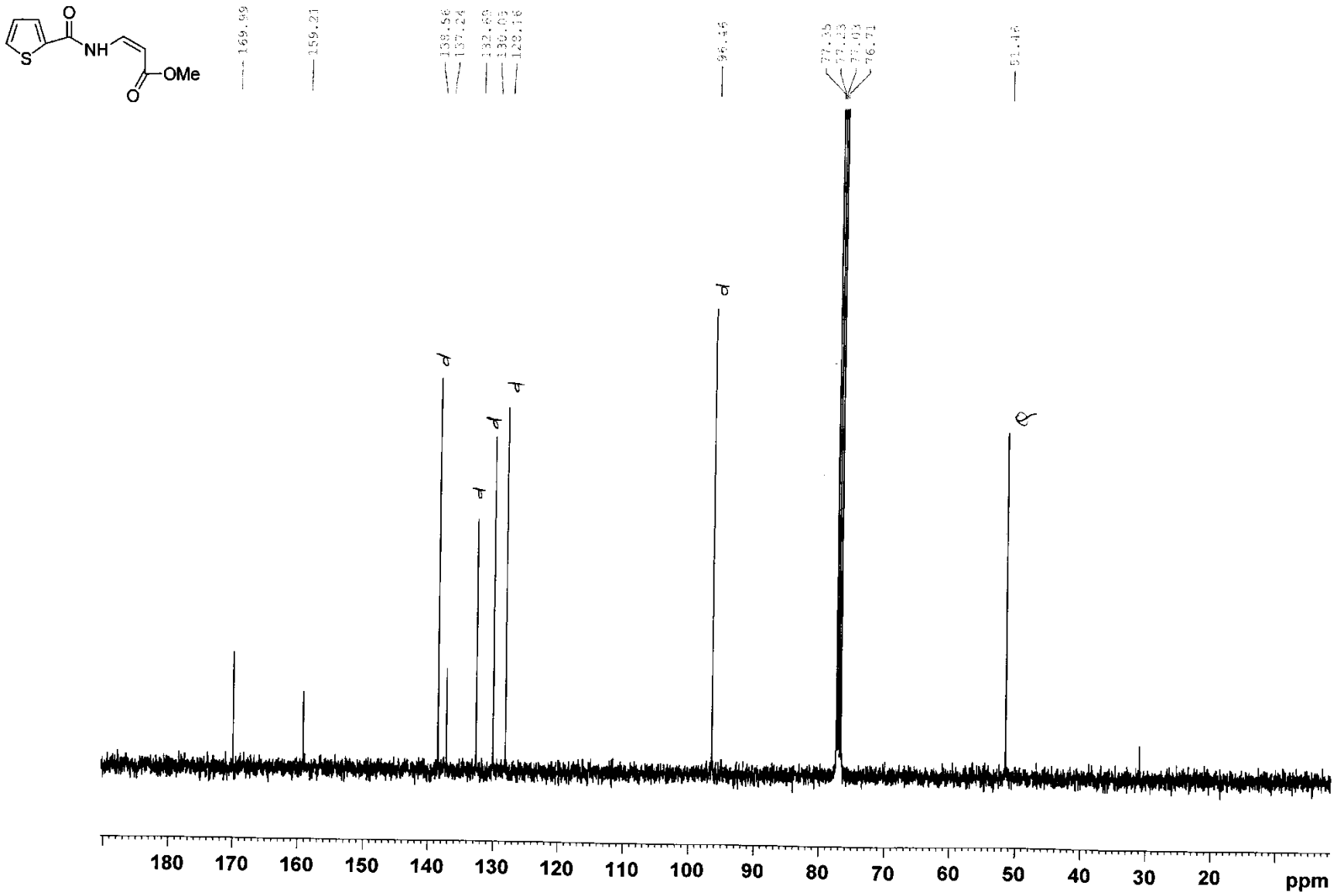
166.41
137.70
133.15
132.48
131.51
130.80
130.51
127.54
97.69
77.34
77.22
77.02
76.70
51.44
Cl
O
N
H
O
OMe
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

NP-MR-270-1H
11.387
11.365
7.749
7.746
7.739
7.737
7.718
7.695
7.690
7.668
7.657
7.655
7.645
7.643
7.281
7.184
7.174
7.172
7.162
5.284
5.262
3.795
2.192
1.657
1.265
0.97
2.99
0.99
1.00
3.12
0.68
ppm
NH
OMe
O
S

NP-MR-270-13C


O
NH
S
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O
169.99
159.21
139.56
137.24
132.69
130.03
128.18
96.45
77.35
77.23
77.03
76.71
51.46
d
d
d
d
d
q
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

NP-MR-334
OMe
N
Me
O
O
O
8.263
8.232
7.281
5.132
5.097
3.720
3.056
1.521
ppm
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2
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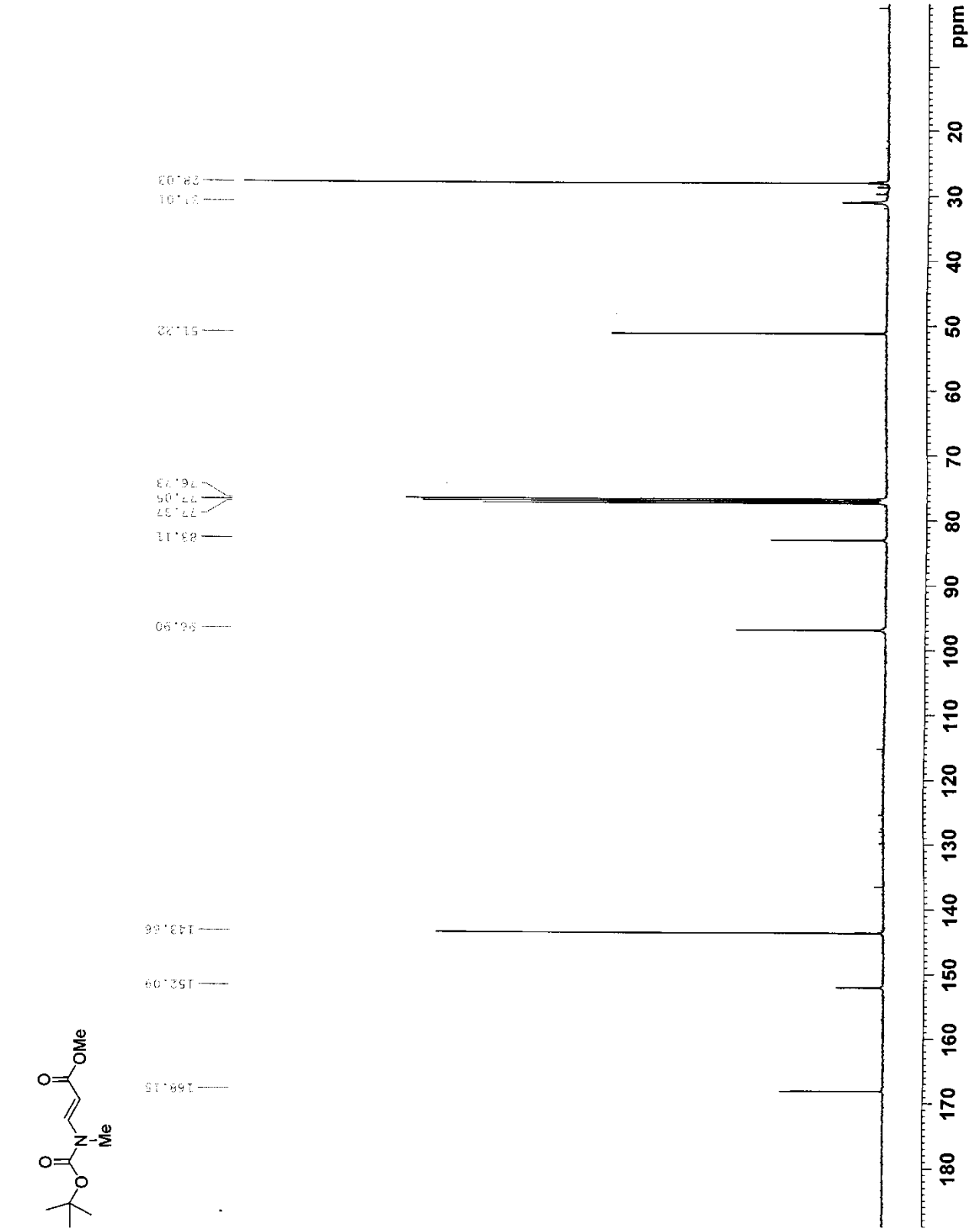
4
5
6
7
8
9
10
9.83
3.15
3.19
1.00
0.14
0.91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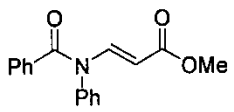
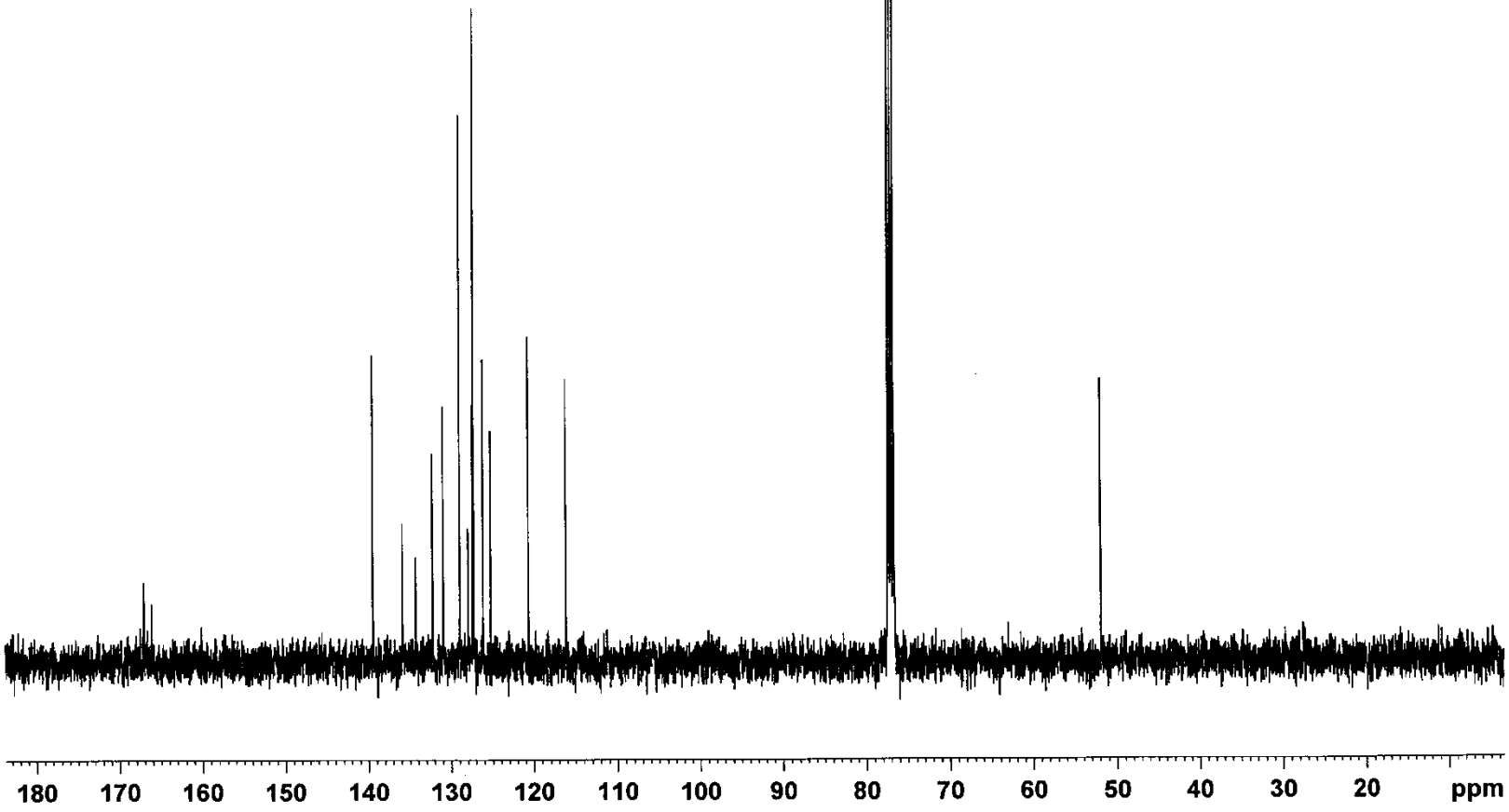
31.01
51.22
76.73
77.04
77.37
83.18
96.90
143.66
152.09
168.15
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
OMe
N
Me
O
O
O

7.938
7.920
7.915
7.898
7.874
7.636
7.633
7.626
7.614
7.608
7.590
7.552
7.532
7.515
7.488
7.471
7.452
7.301
7.282
6.710
6.486
6.447
3.806
1.656
OMe
O
N
Ph
Ph
O
ppm
1
2
3
4
5
6
7
8
9
10
3.00
0.95
0.71
1.01
5.10
4.95

NP-MR-282-13C



167.10
166.16
139.43
135.88
134.26
132.22
130.65
128.94
127.95
127.39
127.76
126.15
125.29
120.84
116.13
77.34
77.02
76.71
51.90



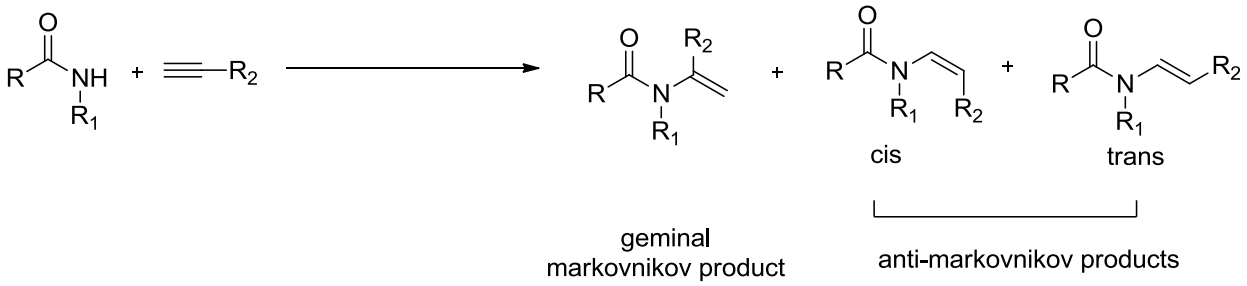
Chapter 3

Stereoselective Synthesis of Enamides by Pd-Catalyzed Hydroamidation of Electron Deficient Terminal Alkynes

3.1 Introduction

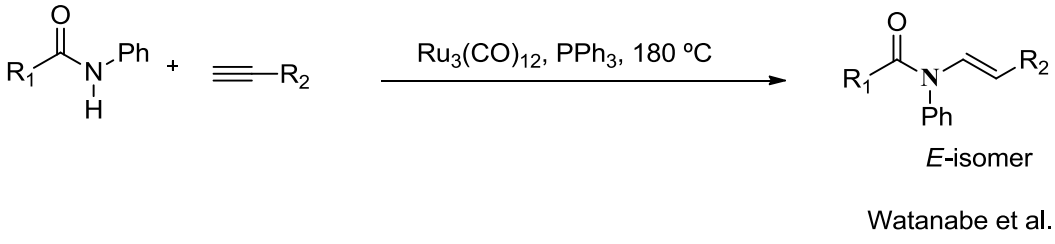
An addition of amides to terminal alkynes, known as hydroamidation, has emerged as an appealing atom-economic approach to access enamides. Hydroamidation of terminal alkynes may give three isomers (Scheme 1), one Markovnikov product and two anti-Markovnikov products (*E*- and *Z*- isomers).[1]

Scheme 1



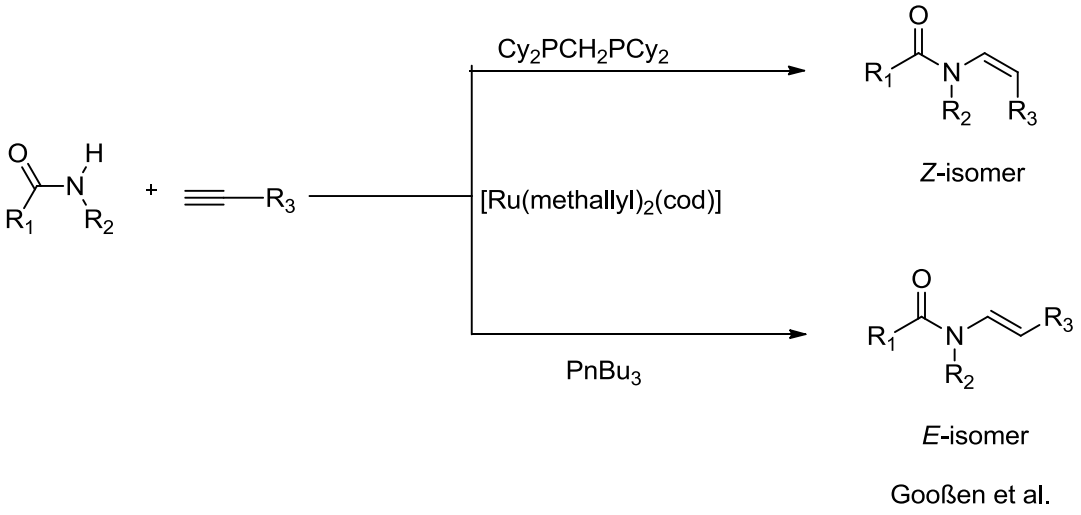
Indeed, this process is triggered by the transition metal catalyst. To date, several catalysts of Ru and Re metals are used potentially for the hydroamidation of alkynes to produce enamides. Evidently, the first example on hydroamidation was reported by Watanabe and co-workers in 1995. They described ruthenium carbonyl $Ru_3(CO)_{12}$-mediated cross-coupling of secondary amides with the terminal alkynes in the presence of Ph_3P ligand to produce *E*-enamides (Scheme 2).[2]

Scheme 2



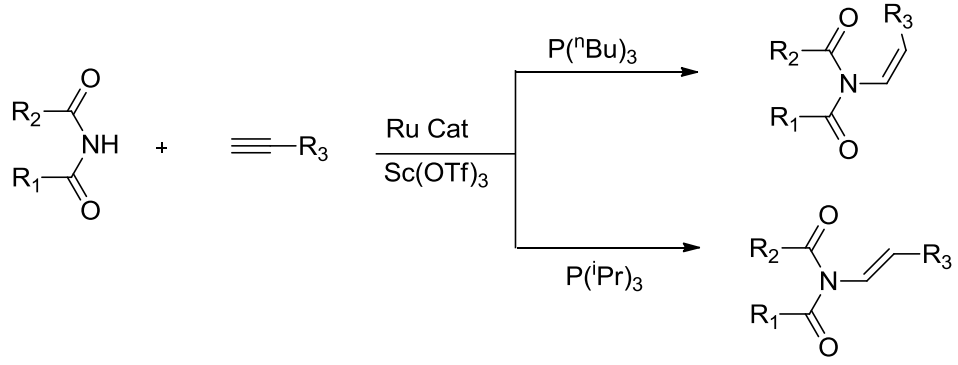
In 2005, Gooßen and co-workers developed ligand-mediated Ru-catalyzed hydroamidation reactions that allow the anti-Markovnikov addition of various N−H nucleophiles to terminal acetylenes for the selective formation of either *E*- or *Z*-configured enamide derivatives (Scheme 3).[3] The stereoselectivity of product is largely dependent on the nature of ligand chosen for the ruthenium catalyst.

Scheme 3



In 2006, Gooßen et al. also described direct addition of imides to terminal alkynes using ruthenium catalyst to afford *E*- and *Z*-anti-Markovnikov products in the presence of Scandium(III) trifluoromethane sulfonate and phosphine ligand in DMF at 60 °C (Scheme 4).[4] The stereoselectivity of the reaction largely depends upon the nature of phosphine ligands.

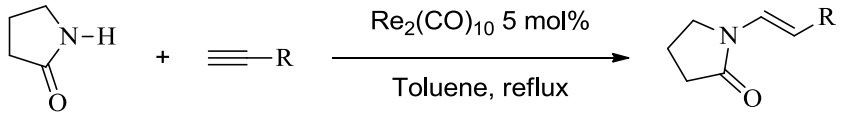
Scheme 4



Takai and co-workers also developed $Re_2(CO)_{10}$ catalyzed hydroamidation of unactivated terminal alkynes for the synthesis of *E*-enamides (Scheme 5).[5] They used commercially available rhenium catalyst for the C-N bond formation to afford enamides without using any ligand or additive. However, this rhenium catalyzed hydroamidation method is limited to cyclic amides and electron rich aliphatic terminal alkynes. The plausible mechanism involves two possibility, one: activation of a C-C triple bond by σ-coordination of the alkyne moiety to the metal center, which subsequently forms rhenium vinylidene intermediate **I**. Intramolecular nucleophilic attack of the amide group to **I**, gives **II**. Reductive elimination of rhenium from **II** gives enamide and regenerates the rhenium catalyst for next catalytic cycle

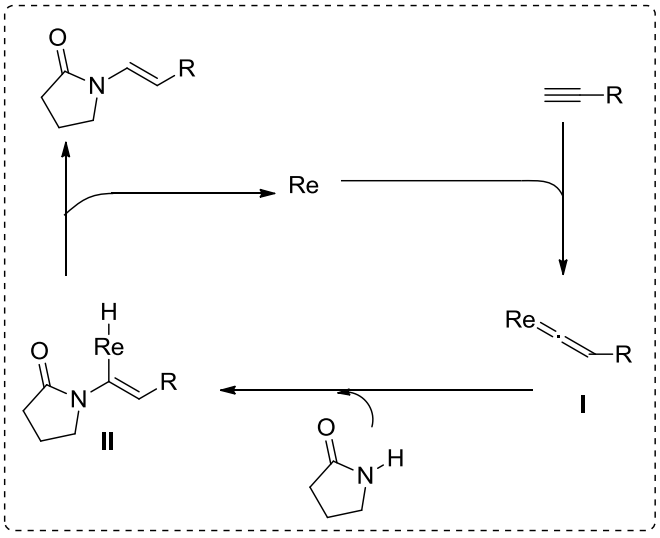
(Scheme 6). Another possibility is the oxidative addition of the amide group followed by the insertion of the alkyne moiety into the rhenium-amide complex.

Scheme 5



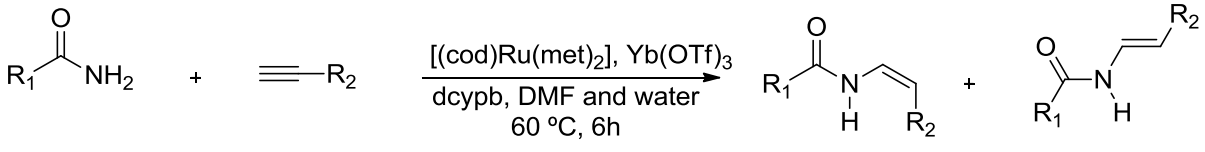
Takai et al.

Scheme 6



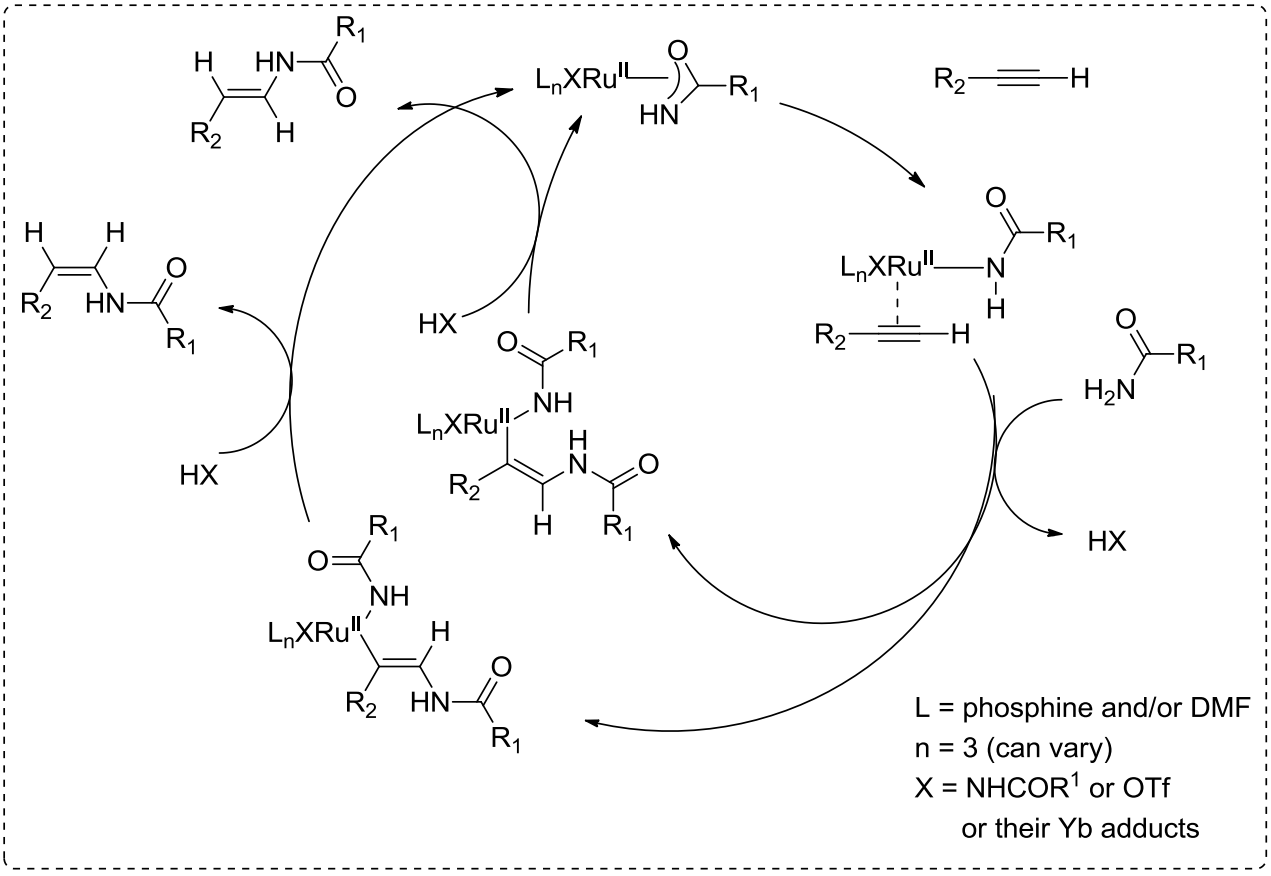
In 2008, Gooßen and co-workers again reported another general method using ruthenium catalyst for the synthesis of stereoselective secondary enamides by addition of amides to alkynes (Scheme 7).[6] In this method, various primary amides were reacted with phenyl acetylene using ruthenium catalyzed anti-markovnikov hydroamidation procedure. A range of alkynes such as aliphatic alkynes, alicyclic alkynes, halo alkyl and aromatic alkyne derivatives were found to be compatible with benzamide to afford the mixture of enamides. Proposed catalytic cycle for the same is depicted as follows (Scheme 8).

Scheme 7



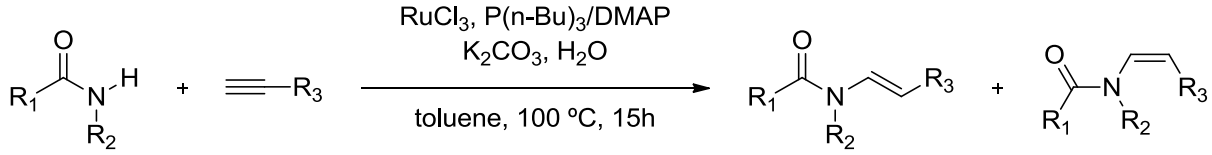
Gooßen et al.

Scheme 8: Possible reaction mechanism



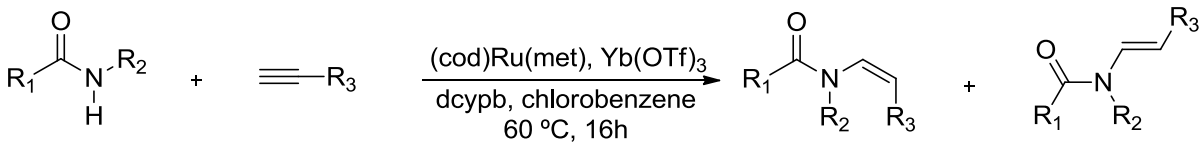
Besides, in the same year, Gooßen et al. used a further simpler catalytic system, such as ruthenium(III) chloride/ tri-n-butyl phosphine/ DMAP in the presence of K_2CO_3 for the synthesis of enamides from secondary amides as well as carbamates (Scheme 9).[7]

Scheme 9



In 2011, the same group also introduced ytterbium triflate along with Ru-catalyst in chlorobenzene to produce enamides from secondary amides (Scheme 10).[8]

Scheme 10



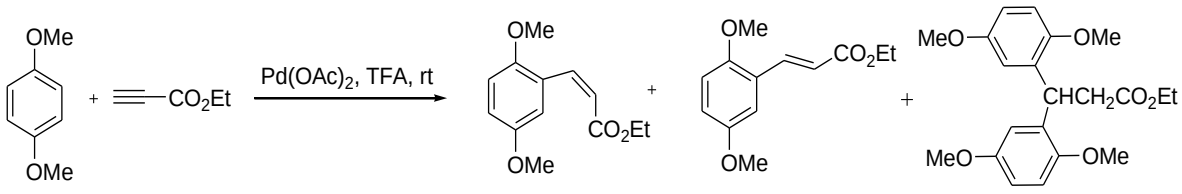
Gooßen et al.

From the above literature report, it is evident that Ru/Re- catalysts were used successfully for hydroamidation reactions. Furthermore, the reported hydroamidation processes are endowed with the use of inactivated terminal alkynes, the often formation of doubly vinylated enamides and ligand-dependent stereoselectivity. Reportedly, the enamides synthesized by later methods often undergo double bond isomerization to thermodynamically more stable *E*-enamides.[6] Surprisingly, use of electron deficient terminal alkynes as coupling partner in the hydroamidation process was not yet precedent. Therefore, development of mild and efficient methods for the stereoselective synthesis of *Z*-enamides from such alkynes is particularly interesting. In continuation of our present interest in the stereoselective synthesis of enamides, we herein report a mild and efficient Pd-catalyzed hydroamidation protocol for the stereoselective synthesis of *Z*-enamides from the electron deficient terminal alkynes through N−C cross-coupling reactions. Moreover, this method is found to be very practical and results in the thermodynamically less favored *Z*-enamides selectively from the primary amides. To the best of our knowledge, this is the first report on Pd-catalyzed hydroamidation of terminal alkynes to enamide.

3.2 Results and Discussion

Our strategy originated from the seminal work of Fujiwara[9] and Kitamura,[10] They have described the Pd-catalyzed coupling of ethyl propiolate with electron rich arenes through C−H activation (Scheme 11). It occurred to us that the use of amide as nucleophile instead of electron rich arene may lead to vinyl−palladium complex, which on subsequent protodepalladation in the presence of Brønsted acid would afford the enamide.

Scheme 11

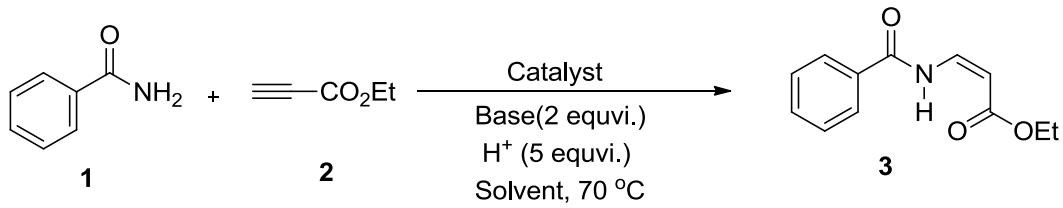


Unlike Fujiwara's report, the possible intramolecular hydrogen bonding between the amido proton and carbonyl oxygen of electron deficient alkyne in the vinyl−palladium complex would eventually attribute to the *Z*-selectivity of the resulting enamide. With this in mind, we began our study using benzamide and ethyl propiolate as the model substrates. Unfortunately, under similar conditions as reported by Fujiwara (i.e., $Pd(OAc)_2/CF_3CO_2H$) no trace of enamide **3** was obtained even at higher temperature (70 °C) with recovery of

starting material (Table 1, entry 1). However, an addition of 2 equiv of a base such as NaOMe furnished the *Z*-enamide **3** as the major product in appreciable yield (44%) at 70 °C (entry 2).

The appearance of doublets at δ 11.5 (for N−H) and 5.27 (vinylic proton) with coupling constant 8.8 Hz, reveals the formation of *Z*- enamide. Optimization studies were then performed that varied the nature of bases, solvents and added acids. These investigations revealed that the utilization of two equiv of sodium acetate (NaOAc) gave enamide **3** (82% yield) over a period of 12 h at 70 °C in toluene. No trace of *E*-enamide was indentified from TLC as well as ^{1}H NMR. Decreasing as well as increasing the temperature lead to the poor yield of enamide. Furthermore, polar solvents such as DMF, THF, CH_3CN and 1,4-dioxane resulted no or poor yield of the isomeric mixture (entries 18−21). A satisfactory result was obtained when DCE was used: enamide **3** was isolated in 72% yield (*Z/E* 2:1 from ^{1}H NMR) (entry 17).

Table 1



1 2 3

Entry	Catalyst	Acid	solvent	Additive	% Yield(Z/E)
1	$Pd(OAc)_2$	CF_3COOH	toluene	nil	0
2	$Pd(OAc)_2$	CF_3COOH	toluene	NaOMe	44
3	**$Pd(OAc)_2$**	**CF_3COOH**	**toluene**	**NaOAc**	**82**
4	$PdCl_2$	CF_3COOH	toluene	NaOAc	31
5	$Pd(pph_3)_2Cl_2$	CF_3COOH	toluene	NaOAc	68
6	$Pd(pph_3)_2(OAc)_2$	CF_3COOH	toluene	NaOAc	56
7	$Pd(CF_3CO_2)_2$	CF_3COOH	toluene	NaOAc	72
8	$Pd(dba)_2$	CF_3COOH	toluene	NaOAc	16
9	$Pd(pph_3)_4$	CF_3COOH	toluene	NaOAc	0
10	Pd/C	CF_3COOH	toluene	NaOAc	0

11	$Pd(OAc)_2$	CH_3COOH	toluene	NaOAc	26
12	$Pd(OAc)_2$	PivOH	toluene	NaOAc	<5
13	$Pd(OAc)_2$	Nil	toluene	NaOAc	0
14	$Pd(OAc)_2$	CF_3COOH	toluene	^tBuOK	<10
15	$Pd(OAc)_2$	CF_3COOH	toluene	NaOH	0
16	$Pd(OAc)_2$	CF_3COOH	toluene	Cs2CO3	15
17	$Pd(OAc)_2$	CF_3COOH	DCE	NaOAc	72(2:1)
18	$Pd(OAc)_2$	CF_3COOH	dioxane	NaOAc	39(1.8:1)
19	$Pd(OAc)_2$	CF_3COOH	CH3CN	NaOAc	15(1:1.2)
20	$Pd(OAc)_2$	CF_3COOH	DMF	NaOAc	0
21	$Pd(OAc)_2$	CF_3COOH	THF	NaOAc	0

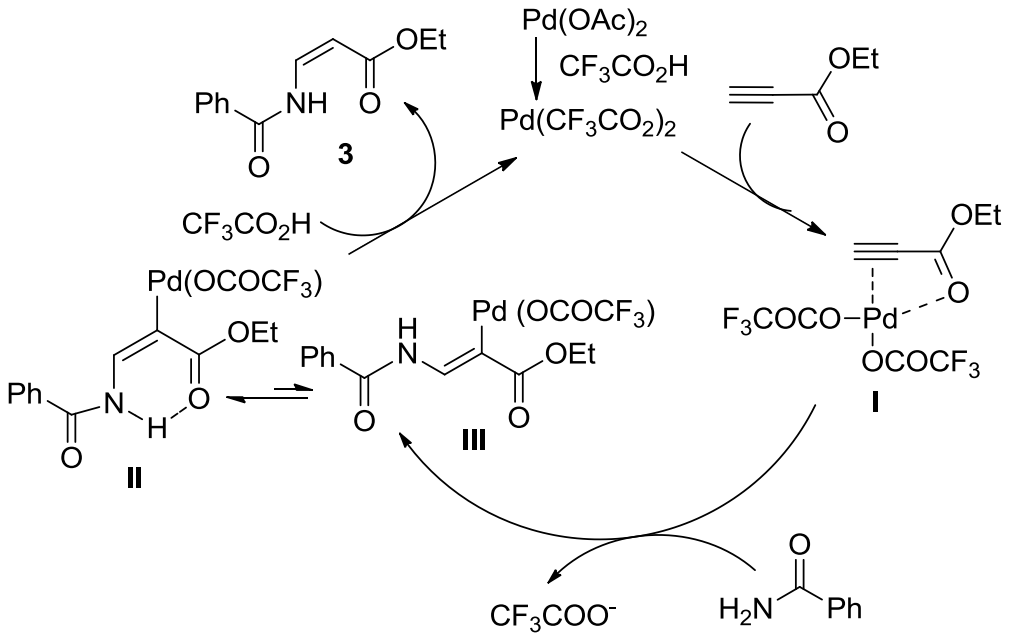
Reaction conditions: A mixture of benzamide (100 mg, 0.82 mmol), ethyl propiolate (0.12 mL, 1.23 mmol), Pd-catalyst (1 mol %), Brønsted acid (5 equiv) and additive (2 equiv) in the indicated solvent were heated at 70 °C for 12 h under N_2 atmosphere.

The use of other bases such as ^tBuOK, NaOH, Cs_2CO_3 resulted in the lower yield. Excess of trifluoroacetic acid (5 equiv) was found to be essential for the completion of the reaction. 1 mol % of $Pd(OAc)_2$ was confirmed to be optimal. An increase in catalyst concentration from 1 to 5 mol% afforded the product in lower yield due to unwanted polymerization/decomposition. The catalytic efficiencies of other Pd-catalysts were also examined, and it revealed that among the tested catalysts (i.e., $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_2(OAC)_2$, $Pd(TFA)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$ and Pd/C), $Pd(OAc)_2$ displayed higher activity under the same experimental conditions (entries 3−10).

The plausible mechanism

A plausible pathway for the selective synthesis of *Z*-enamide **3** is outlined in Scheme 12, although numerous details remain to be elucidated.

Scheme 12: The plausible mechanism



The reaction of benzamide with ethyl propiolate in the absence of trifloroacetic acid did not result any enamide (entry 13). Furthermore, this cross-coupling in presence of acetic acid resulted only 26% of the enamide (entry 11), whereas the cross-coupling in the presence of $Pd(CF_3COO)_2$ afforded 72% yield of enamide (entry 7). It indicates that at optimum reaction conditions, like earlier observations of Fujiwara[9] and Kitamura,[10] $Pd(OAc)_2$ reacts with CF_3CO_2H and leads to the more reactive $Pd(CF_3COO)_2$. The addition of the latter to the activated alkyne leads to the alkyne-palladium complex **(I**). Nucleophilic attack of amide nitrogen to **I** results in the vinyl-palladium complex (**II** and/or **III**). As expected, like Chang's[11] and our report,[12] the possible hydrogen bonding between the carbonyl oxygen of alkyne and the N−H of amide (C=O•••H-N) provides the additional stability to the complex and thus drives the equilibrium toward **II**. This intramolecular H-bonding attributes to the excellent *Z*-selectivity of the hydroamidation reaction. Furthermore, in the presence of an excess of Brønsted acid, **II** undergoes protodepalladation[13,14] readily and affords the *Z*-enamide selectively.

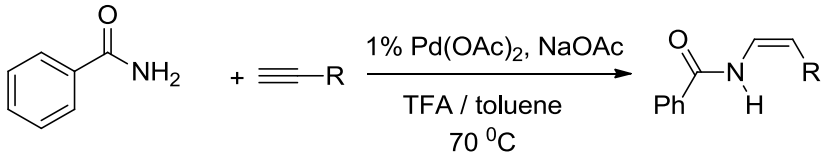
Substrate Scope

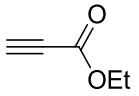
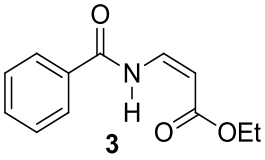
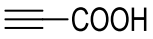
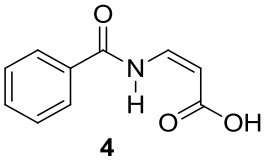
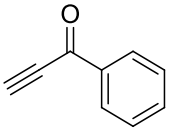
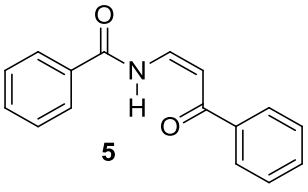
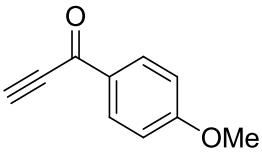
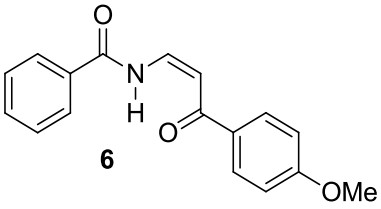
Having the optimal conditions, the scope of alkyne component was explored with different substitutions. It revealed that electron-withdrawing substitutions like −COOH, COAr to the alkyne, resulted Z-enamides selectively in modest yield (Table 2). Unactivated

alkynes such as phenylacetylene and 1-octyne are inactive to afford the enamide, albeit the homocoupling of alkynes were resulted.

Next, we investigated the scope and limitation of the catalytic process with various amides, and the results are summarized in Table 3. Pleasingly, this catalytic protocol was found to be tolerant to both electron-donating and -withdrawing aryl ring substitutions, and in most cases moderate to good yields of enamides was obtained. As such, electron-withdrawing substituents (i.e., −NO2, Cl) to the aromatic ring that decrease the nucleophilicity of amide still participated in cross-coupling with ethyl propiolate and lead to the *Z*-enamides in good yield without affecting the selectivity. Heteroaryl amides also afforded the corresponding enamides in good yield with retention of *Z*-selectivity.

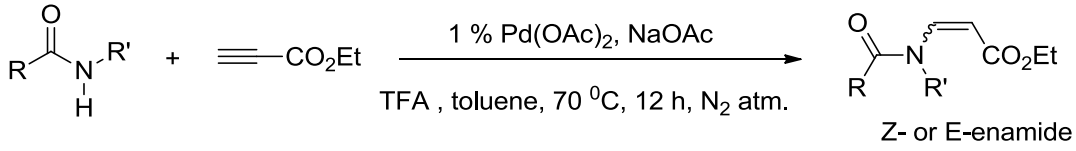
Table 2

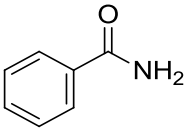
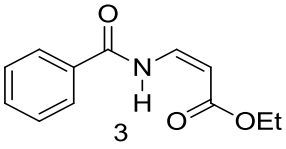
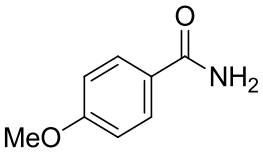
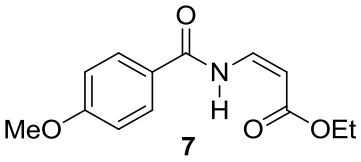
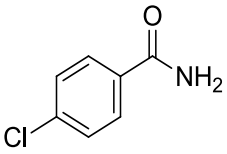
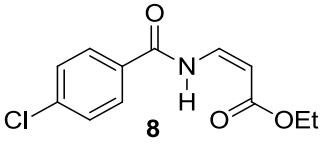
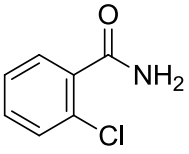
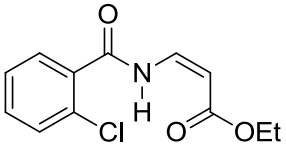
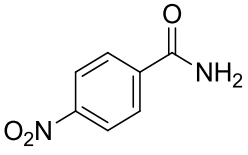
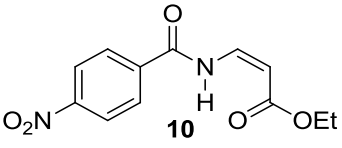
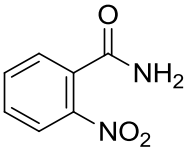
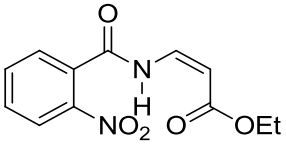


Entry	Substrate	Product	% Yield
1		 **3**	82
2		 **4**	60
3		 **5**	43
4		 **6**	45

Reaction conditions: amide (1 equiv.), alkyne (1.5 equiv.), TFA (5equiv.), $Pd(OAc)_2$ (1 mol%), NaOAc (2 equiv.)70 °C for 12 h under N_2atmosphere

Table 3



Entry	Substrate	Product	% Yield
1		 **3**	82
2		 **7**	68
3		 **8**	62
4		 **9**	56
5		 **10**	72
6		 **11**	50

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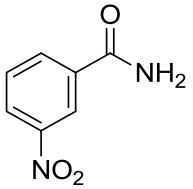
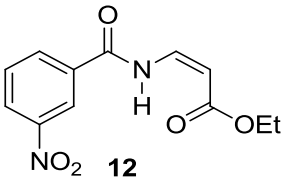
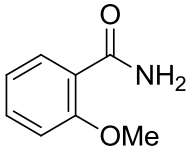
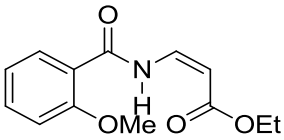
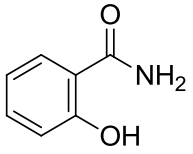
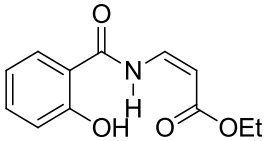
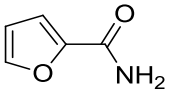
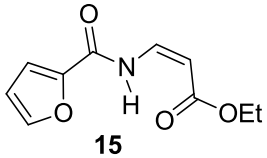
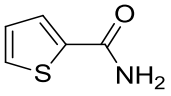
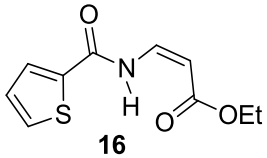
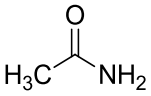
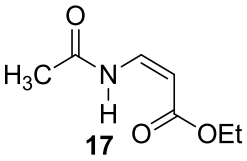
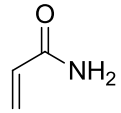
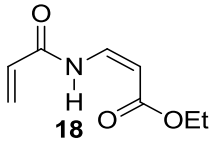
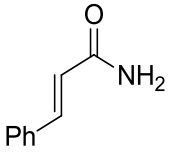
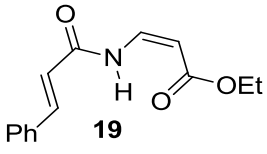
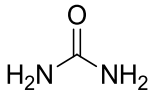
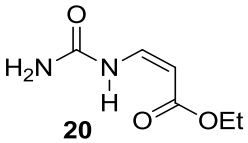
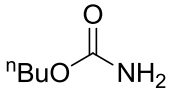
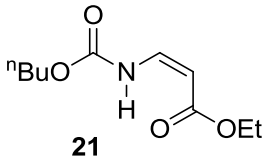
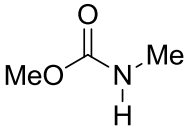
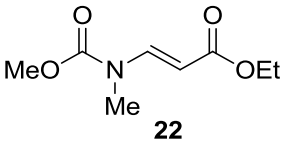
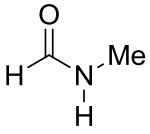
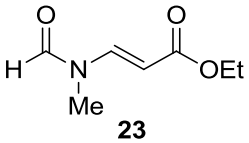
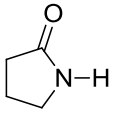
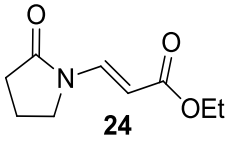
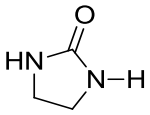
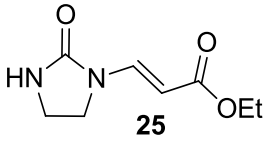
7		 **12**	56
8		 **13**	75
9		 **14**	56
10		 **15**	67
11		 **16**	60
12		 **17**	52
13		 **18**	55
14		 **19**	52

Continued….

15		 **20**	46
16		 **21**	54
17		 **22**	56
18		 **23**	41
19		 **24**	72
20		 **25**	54

Reaction conditions: amide (1 equiv.), alkyne (1.5 equiv.), TFA (5equiv.), $Pd(OAc)_2$ (1 mol%), NaOAc (2 equiv.)70 °C for 12 h under N_2atmosphere

Amides with an alkyl group, carbamate and urea are found to be reactive to ethyl propiolate and resulted *Z*-enamides selectively. However, when secondary amides were used, tertiary enamides with *E*-selectivity (J = 14.4 Hz) resulted in modest yield. Cyclic amides such as pyrrolidinone, ethylene urea were also undergone hydroamidation reaction and furnished the *E*-enamides in appreciable yield. Selective formation of *E*-enamide is due to the lack of intramolecular hydrogen bonding in the vinyl−palladium complex that drives the equilibrium toward the thermodynamically more stable intermediate (e.g., III, Scheme 12).

3.3 Conclusions

The first Pd-catalyzed hydroamidation of activated terminal alkynes is presented. The conditions can be applied to a number of amides as well as electron deficient alkynes with good functional group tolerance. The reaction is stereoselective: primary amides give *Z*-enamides, whereas secondary amides give *E*-enamides selectively. The high stereoselectivity is possibly due to the favorable intramolecular hydrogen bonding between the carbonyl oxygen of alkyne and the N−H of the amide in the vinyl palladium complex. This methodology is simple and allows access to varieties of enamides with high stereoselectivity.

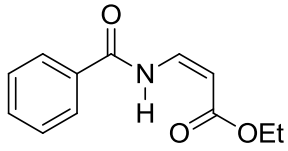
3.4 Experimental

General Procedure for Enamide Synthesis from Alkyne

Method A: An oven-dried round-bottom flask was charged with amide. (100mg), $Pd(OAc)_2$ (1 mol %), trifluoroacetic acid (5 equiv), NaOAc(2 equiv), and toluene (4 mL). The reaction mixture was stirred for 5min under nitrogen atmosphere at room temperature, and then ethyl propiolate (1.5 equiv) was added dropwise. The reaction mixture was then stirred for 5 min, and then the temperature was raised to 70 °C. After12 h, the reaction mixture was diluted with ethyl acetate followed by water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over the brine, anhydrous Na_2SO_4, and then evaporated under reduced pressure. The crude residue was purified by column chromatography over the silica gel using the mixture of petroleum ether and ethyl acetate aseluent to give the pure enamide.

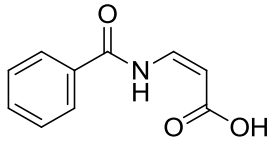
Method B: An oven-dried round-bottom flask was charged with amide (100 mg), $Pd(OAc)_2$ (1 mol %), trifluoroacetic acid (5 equiv), NaOAc (2 equiv), and toluene (4 mL). The reaction mixture was stirred for 5 min under nitrogen atmosphere at room temperature, and then ethyl propiolate (1.5 equiv) was added dropwise. The reaction mixture was stirred for 36 h at room temperature (rt) and then diluted with ethyl acetate followed by water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over brine, anhydrous Na_2SO_4, and then evaporated under reduced pressure. The crude residue was purified by column chromatography over silica gel using the mixture of petroleum ether and ethyl acetate as eluent to give the pure enamide.

(*Z*)-Ethyl 3-(benzamido)acrylate(3)[11]



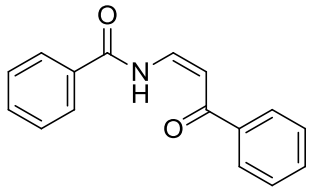
3 was obtained following general procedure (Method A) as a white crystalline solid(179 mg, 82% yield): mp 76−77 °C; IR (KBr) 3324, 2955, 1684,1638, 1581, 1508, 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54(d, 1H, *J* = 9.6 Hz), 7.98−7.95 (m, 2H), 7.76 (dd, 1H, J_1 = 11.2 Hz, J_2= 8.8 Hz), 7.64−7.58 (m, 2H), 7.55−7.49 (m, 2H), 5.28 (d, 1H, *J* =8.4 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 164.5, 138.7, 132.9, 132.1, 128.9, 127.7, 97.1, 60.3, 14.2; MS (ESI, −Ve)m/z (relative intensity) 217.90 ([M − H]+, 100%). Anal. Calcd for$C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.40; H, 5.68; N, 6.09.

(*Z*)-3-(Benzamido)acrylic acid (4)



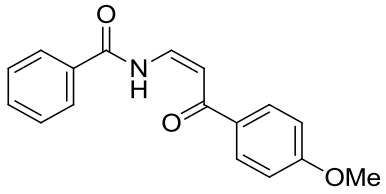
4 was obtained following general procedure (Method **A**) as a white crystalline solid (114 mg,60% yield): mp 163−165 °C; IR (KBr) 3327, 3036, 2997, 1697, 1671,1594, 1402, 1239 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (d, 1H,*J* = 10.8 Hz), 7.98−7.85 (m, 3H), 7.68−7.60 (m, 1H), 7.59−7.50 (m,2H), 7.09−7.03 (m, 1H), 5.34 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.9, 164.5, 141.1, 133.3, 131.9,129.0, 127.7, 95.7; MS (ESI, −ve) m/z (relative intensity)190.04 ([M − H]+, 100%). Anal. Calcd for $C_{10}H_9NO_3$: C 62.82; H4.74; N 7.33. Found: C 62.61; H 4.69; N 7.63.

***N*-((*Z*)-3-Oxo-3-phenylprop-1-enyl)benzamide(5)**



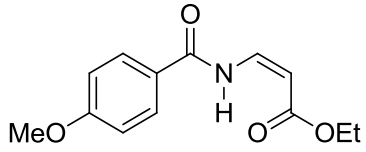
5 was obtained following general procedure (Method **A**) as a white crystalline solid (89 mg, 43% yield): mp 102−104 °C; IR (KBr)3338, 3063, 2912, 2858, 1692, 1638, 1585, 1384, 1234, 1012 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 12.95 (d, 1H, *J* = 9.2 Hz,), 8.10−8.07 (m,2H), 8.02−7.90 (m, 3H), 7.66−7.48 (m, 6H), 6.43 (d, 1H, *J* = 8.4Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 165.3, 140.1,138.1, 133.1, 132.9, 132.0, 128.9, 128.7, 128.0,127.9, 100.8; MS (ESI, −ve) m/z (relative intensity) 250.06([M − H]+, 100%).

***N*-((Z)-3-(4-Methoxyphenyl)-3-oxoprop-1-enyl)benzamide (6)**



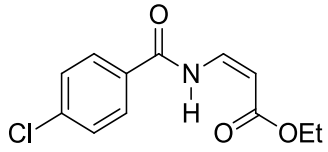
6 was obtained following general procedure (Method **A**) as a white crystalline solid (104 mg, 45% yield): mp 86−88 °C; IR (KBr) 3338,3063, 2912, 2858, 1692, 1638, 1585, 1384, 1234, 1012 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 12.98 (d, 1H, *J* = 10 Hz), 8.13−8.05 (m, 2H),8.03−7.96 (m, 2H), 7.92 (dd, 1H, J_1 = 10.8 Hz, J_2 = 8.8 Hz, 1H),7.65−7.60 (m, 1H), 7.58−7.53 (m, 2H), 7.02−6.98 (m, 2H), 6.40 (d,1H, *J* = 8.8 Hz), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 165.3, 163.5, 139.4, 133.0, 132.1, 131.0, 130.2, 128.9, 127.9, 113.9, 100.8, 55.5; MS(ESI, −ve) m/z (relative intensity) 280.09 ([M − H]+, 100%). Anal.Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; O, 17.06. Found: C, 72.65; H, 5.33; N, 5.05.

(*Z*)-Ethyl 3-(4-methoxybenzamido)acrylate (7)



7 was obtained following general procedure (Method **A**) as a white crystalline solid(169 mg, 68% yield): mp 100−102 °C; IR (KBr) 3433, 2998, 2967,2924, 1670, 1622, 1479, 1369 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ11.46 (d, 1H, *J* = 10.8 Hz), 7.94 (d, 2H, *J* = 8.8 Hz), 7.75 (dd, 1H, J_1 =11.2 Hz, J_2 = 8.8 Hz), 6.99 (d, 2H, *J* = 8.8 Hz), 5.24 (d, 1H, *J* = 9.2Hz), 4.25 (q, 2H, *J* = 6.8 Hz) 3.89 (s, 3H), 1.35 (t, 3H, *J* = 7.2 Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 163.9, 163.3, 139.0, 129.7, 124.5, 114.1, 96.4, 60.1, 55.4, 14.2; MS (ESI, −Ve) m/z (relative intensity) 248.13 ([M − H]+,100%). Anal. Calcd for $C_{13}H_{15}NO_4$: C 62.64; H 6.07; N 5.62. Found:C 62.69; H 6.00; N 5.53.

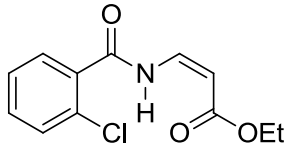
(*Z*)-Ethyl 3-(4-chlorobenzamido)acrylate (8)



8 was obtained following general procedure (Method **A**) as yellow solid (157 mg, 62%yield): mp 52−54 °C; IR (KBr) 3290, 2932, 1702, 1678, 1639, 1590,1509, 1486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.54 (d, 1H, *J* = 10Hz), 7.93−7.88 (m, 2H), 7.73 (dd, 1H, J_1 = 11.2 Hz, J_2 =

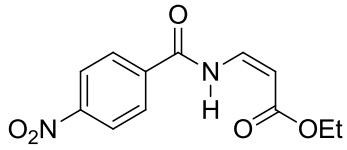
8.8 Hz),7.50−7.46 (m, 2H), 5.29 (d, 1H, *J* = 8.8 Hz), 4.25 (q, 2H, *J* = 7.2 Hz),1.35 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7,163.4, 139.3, 138.6, 130.6, 129.2, 129.1, 97.5, 60.4, 14.2; MS (ESI, −ve) m/z (relative intensity) 252.14([M − H]+, 100%). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77;N, 5.52. Found: C, 56.78; H, 4.68; N, 5.72.

(*Z*)-Ethyl 3-(2-chlorobenzamide)acrylate (9)



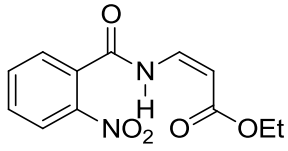
9 was obtained following general procedure (Method **A**) as a white crystalline solid(141 mg, 56% yield): mp 85−87 °C; IR (KBr) 3313, 3071, 2981,2940, 2901, 1723, 1685, 1628, 1592, 1481, 1434, 1379, 1256, 1201,1139, 1094, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (d, 1H,*J* = 8.8 Hz), 7.75−7.66 (m, 2H), 7.52−7.41 (m, 2H), 7.40−7.34 (m,1H), 5.27 (d, 1H, *J* = 9.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* =7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (s), 164.3, 137.4, 133.2, 132.3, 131.5, 130.7, 130.5, 127.1,98.1, 60.2, 14.2; MS (ESI, −ve) m/z (relative intensity) 252.16 ([M − H]+, 100%). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C 56.81; H4.77; N 5.52. Found: C 57.02; H 5.00; N 5.92.

(*Z*)-Ethyl 3-(4-nitrobenzamido)acrylate (10)



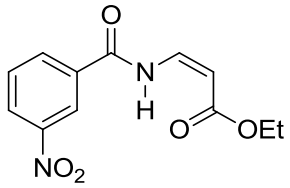
10 was obtained following general procedure (Method **A**) as yellow solid (190 mg, 72%yield): mp 127−129 °C; IR (KBr) 3437, 2990, 2912, 1687, 1670,1628, 1527, 1477, 1346 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69(d, 1H, *J* = 10 Hz), 8.37−8.33 (m, 2H), 8.14−8.10 (m, 2H), 7.72 (dd,1H, J_1= 10.8 Hz, J_2= 8.8 Hz), 5.36 (d, 1H, *J* = 8.8 Hz), 4.25 (q, 2H, *J* =7.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ169.6, 162.5, 150.3, 138.0, 137.6, 128.8, 124.0, 98.8, 60.6, 14.2; MS (ES-APCI, +ve) m/z (relativeintensity) 265 ([M + H]+, 100%). Anal. Calcd for $C_{12}H_{12}N_2O_5$: C54.55; H 4.58; N 10.60. Found: C 54.32; H 4.70; N 10.44.

(*Z*)-Ethyl 3-(2-nitrobenzamido)acrylate (11)



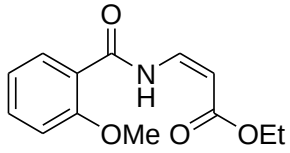
11 was obtained following general procedure (Method **A**) as a white crystalline solid(132 mg, 50% yield): mp 108−109 °C; IR (KBr) 3464, 3319, 3071,2986, 2955, 1687, 1627, 1532, 1353, 1221, 1024 cm^{-1};^{1}H NMR (400MHz, $CDCl_3$) δ 11.71 (d, 1H, *J* = 10.0 Hz), 8.85−8.82 (m, 1H),8.48−8.44 (m, 1H), 8.27−8.23 (m, 1H), 7.78−7.71 (m, 2H), 5.36 (d,1H, *J* = 8.8 Hz), 4.27 (q, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.5, 162.3, 148.6, 138.1,134.1, 132.9, 130.1, 127.2, 123.1, 98.7, 60.6,14.2; MS (ESI, −ve) m/z (relative intensity) 262.98 ([M − H]+,100%). Anal. Calcd for $C_{12}H_{12}N_2O_5$: C 54.55; H 4.58; N 10.60.Found: C 54.82; H 4.78; N 10.89.

(*Z*)-Ethyl 3-(3-nitrobenzamido)acrylate (12)



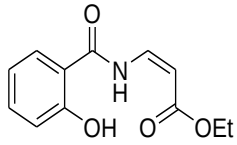
12 was obtained following general procedure (Method **A**) as yellow solid (147 mg, 56%yield): mp 103−105 °C; IR (KBr) 3693, 3292,3063, 2980, 2932, 1682,1630, 1531,1379, 1349, 1202 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ10.92 (d, 1H, *J* = 9.6 Hz), 8.11 (m, 1H), 7.77−7.60 (m, 4H), 5.33 (d,1H, *J* = 8.8 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.1, 163.9, 146.9, 137.4,133.7, 131.4, 131.1, 128.3, 124.8, 98.5, 60.4,14.1; MS (ESI, −ve) m/z (relative intensity) 263.02 ([M − H]+,100%). Anal. Calcd for $C_{12}H_{12}N_2O_5$: C 54.55; H 4.58; N 10.60.Found: C 54.74; H 4.67; N 11.00.

(*Z*)-Ethyl 3-(2-methoxybenzamido)acrylate (13)



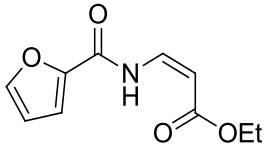
13 was obtained following general procedure (Method **B**) as oil (186 mg, 75% yield):IR (neat) 3442, 3025, 2979, 2846, 1680, 1621, 1481, 1397 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 12.40 (d, 1H, *J* = 9.6 Hz), 8.27−8.22 (m,1H), 7.78 (dd, 1H, J_1 = 11.2 Hz, J_2 = 8.8 Hz), 7.55−7.51 (m, 1H),7.12−6.99 (m, 1H), 5.21 (d, 1H, *J* = 9.2 Hz), 4.25 (q, 2H, *J* = 7.2 Hz),4.12 (s, 3H), 1.32 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.4, 163.6, 158.4, 138.0, 134.2, 132.8, 121.2, 119.8, 111.5, 97.1, 59.7, 55.7, 14.3; MS(ESI, +ve) m/z (relative intensity) 272.02 ([M + Na]+, 100%), 521.10([2M + Na]+, 90%). Anal. Calcd for $C_{13}H_{15}NO_4$: C 62.64; H 6.07; N5.62. Found: C 62.48; H 5.90; N 5.38.

(*Z*)-Ethyl 3-(2-hydroxybenzamido)acrylate(14)



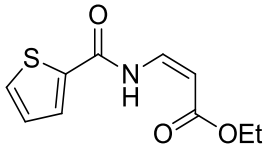
14 was obtained following general procedure (Method **A**) as a white crystalline solid(131 mg, 56% yield): mp 98−100 °C; IR (KBr) 3311, 2956, 1686, 1661, 1636, 1602, 1517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84(s, 1H), 11.75 (d, 1H, J = 9.6 Hz), 7.71 (dd, J_1 = 10.8 Hz, J_2 = 8.8 Hz),7.63−7.59 (m, 1H), 7.52−7.39 (m, 1H), 7.09−7.03 (m, 1H), 7.02−6.92 (m, 1H), 5.33 (d, 1H, J = 8.8 Hz), 4.26 (q, 2H, J = 7.2 Hz), 1.35(t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 167.8, 162.5, 137.4, 135.7, 126.3, 119.3, 118.7,113.0, 98.2, 60.5, 14.2; MS (ESI, −ve) m/z (relativeintensity) 234.09 ([M − H]+, 100%). Anal. Calcd for $C_{12}H_{13}NO_4$: C,61.27; H, 5.57; N, 5.95. Found: C, 61.22; H, 5.74; N, 6.07.

(*Z*)-Ethyl 3-(furan-2-carboxamido)acrylate (15)



15 was obtained following general procedure (Method **A**) as a white crystalline solid (140 mg, 67% yield): mp 83−85 °C; IR (KBr) 3327, 3128, 2978, 2936, 2874, 1725, 1685, 1629, 1587, 1492, 1469 cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 11.38 (d, 1H, J = 8.8 Hz), 7.68−7.58 (m, 2H), 7.31(m, 1H), 6.59−6.56 (m, 1H), 5.26 (d, 1H, J = 8.8 Hz), 4.25 (q, 2H, J =7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ169.1, 155.6, 146.5, 145.6, 137.3, 117.0, 112.6, 97.4, 60.3, 14.2. MS (ESI, +ve) m/z (relative intensity) 210.12 ([M + H]+, 100%). Anal. Calcd for $C_{10}H_{11}NO_4$: C 57.41; H5.30; N 6.70. Found: C 57.59; H 5.18; N 6.58.

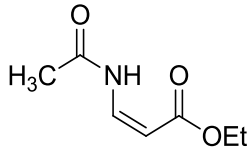
(*Z*)-Ethyl 3-(thiophene-2-carboxamido)acrylate (16)



16 was obtained following general procedure (Method **A**) as a white crystalline solid (135 mg, 60% yield): mp 116−118 °C; IR (KBr) 3335, 3070,2952, 1674, 1627, 1525, 1470, 1425 cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ 11.40 (d, 1H, J = 9.6 Hz), 7.75−7.72 (m, 1H), 7.68 (dd, J_1 =8.8 Hz, J_2 = 5.6 Hz), 7.64−7.62 (m, 1H), 7.18−7.15 (m, 1H), 5.25 (d,1H, J = 8.8 Hz), 4.25 (q, 2H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.5, 159.2, 138.3, 137.3,132.5, 130.0, 128.1, 96.9, 60.3, 14.2; MS (ESI,−ve) m/z (relative

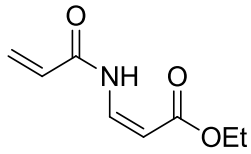
intensity) 224.06 ([M − H]+, 100%). Anal. Calcdfor $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C 53.48; H, 5.27; N, 6.32; S, 14.42.

(*Z*)-Ethyl 3-acetamidoacrylate (17)[11]



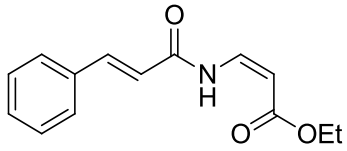
17 was obtained followinggeneral procedure (Method **A**) as oil (81 mg, 52% yield): IR (neat)3325, 2950, 2925, 2850, 1719, 1686, 1630, 1502, 1398, 1386 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.49 (dd, 1H, J_1 = 11.2 Hz,J_2 = 8.8 Hz), 5.09 (d, 1H, J = 9.2 Hz), 4.15 (q, 2H, J = 7.2 Hz), 2.17 (s, 3H), 1.26 (t, 3H, J = 7.2 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.1, 168.5, 137.8, 96.4, 60.1, 23.5, 14.1; MS(ESI, +ve) m/z (relative intensity) 158.06 ([M + H]+, 100%).

(*Z*)-Ethyl 3-(acrylamido)acrylate (18)



18 was obtained following general procedure (Method **A**) as oil (93 mg, 55% yield): IR (neat)3335, 2981, 2940, 1682, 1630, 1480, 1409, 1376 cm^{-1};^{1}H NMR (400MHz, $CDCl_3$) δ 10.68 (bs, 1H), 7.58 (dd, 1H, J_1 = 10.4 Hz, J_2 = 9.2Hz), 6.45 (d, 1H, J = 17.2 Hz), 6.28−6.18 (m, 1H), 5.86 (d, 1H, J =10.4 Hz), 5.19 (d, 1H, J = 8.8 Hz), 4.20 (q, 2H, J = 6.8 Hz), 1.30 (t,3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.2,138.0, 129.9, 129.6, 97.3, 60.2, 14.1; MS (ESI, −ve) m/z (relative intensity) 168 ([M − H]+, 38%). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.91; H, 6.38; N, 8.21.

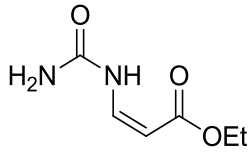
(2*Z*)-Ethyl 3-(cinnamamido)acrylate (19)[11]



19 was obtained following general procedure (Method **A**) as a white crystalline solid (127 mg, 52% yield): mp 112−113 °C; IR (KBr) 3435, 2986, 2936, 1679, 1627, 1479, 1380 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (d, 1H, J = 9.2 Hz), 7.79 (d, 1H, J = 15.6 Hz), 7.67 (dd, 1H, J_1 = 8.8 Hz, J_2= 11.2 Hz), 7.60−7.55 (m, 2H), 7.44−7.39 (m, 3H), 6.54 (d, 1H, J = 15.6 Hz), 5.21 (dd, 1H, J = 8.8 Hz) 4.23 (q, 2H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.5, 144.4, 138.4, 134.2, 130.5, 128.9, 128.2, 119.2, 96.7, 60.2,

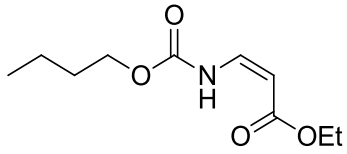
14.2; MS (ESI, −ve) m/z (relative intensity) 243.88 ([M − H]+, 100%). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.36; H, 6.42; N, 6.08.

(*Z*)-Ethyl 3-ureidoacrylate (20)



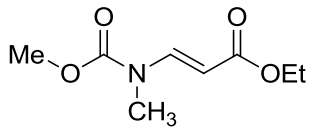
20 was obtained following general procedure (Method **B**) as oil (72 mg, 46% yield): IR (neat) 3431, 3384, 2970, 2924, 2851, 1710, 1656, 1632, 1510, 1463, 1366 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (d, 1H, J = 10 Hz), 7.45 (dd, 1H, J_1 = 11.4 Hz, J_2 = 8.8 Hz), 5.03 (d, 1H, J = 8.8 Hz), 5.04 (s, 2H, -NH2), 4.18 (q, 2H, J = 7.2 Hz), 1.30 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ169.8, 153.7, 140.7, 93.2, 59.9, 14.2; MS (ESI, +ve) m/z (relative intensity) 159 ([M + H]+, 100%), 316 ([2M]+, 30%). Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 45.77; H, 6.29; N, 17.92.

Butyl (*Z*)-2-(ethoxycarbonyl)vinylcarbamate (21)



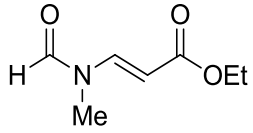
21 was obtained following general procedure (Method **B**) as oil (116 mg, 54% yield): IR (neat) 3716, 3329, 2962, 2874, 1745, 1685, 1633, 1489, 1404, 1370, 1355 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (bs, 1H), 7.27 (m, 1H), 5.03 (d, 1H, J = 8.8 Hz), 4.22−4.12 (m, 4H), 1.69−1.60 (m, 2H), 1.46−1.40 (m, 2H), 1.33 (t, 3H, J = 7.2 Hz), 0.96 (t, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 153.6, 140.1, 94.7, 66.0, 59.9, 30.7, 18.9, 14.2, 13.5; MS (ESI, +ve) m/z (relative intensity) 238.14 ([M + Na]+, 100%). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.85; H, 8.22; N, 6.72.

Methyl (*E*)-2-(ethoxycarbonyl)vinylmethylcarbamate (22)



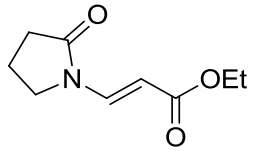
22 was obtained following general procedure (Method **B**) as oil (104 mg, 56% yield): IR (neat) 3098, 2974, 2958, 1733, 1705, 1629, 1446, 1376, 1360 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 5.20 (d, 1H, J = 14.4 Hz), 4.21 (q, 2H, J = 7.2 Hz), 3.86 (s, 3H), 3.13 (s, 3H), 1.28 (q, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 130.1, 128.0, 98.5, 60.0, 54.1, 31.3, 14.3; MS (ESI, +ve) m/z (relative intensity) 187.07 ([M + H]+, 100%). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.42; H, 7.23; N, 7.42.

(*E*)-Ethyl 3-(N-methylformamido)acrylate (23)



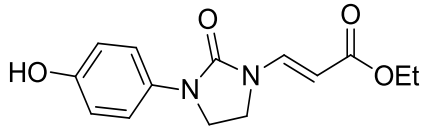
23 was obtained following general procedure (Method **B**) as oil (64 mg, 41% yield): IR (neat) 2980, 2940, 2897, 1711, 1624, 1369 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.82 (d, 1H, *J* = 13.6 Hz), 5.44 (d, 1H, *J* = 14 Hz), 4.23 (q, 2H, *J* = 8 Hz), 3.09 (s, 3H), 1.31 (t, 3H, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 163.1, 143.4, 100.0, 60.4, 27.7, 14.3; MS (ESI, +ve) m/z (relative intensity) 314.30 ([2M]+ 100%). Anal. Calcd for $C_7H_{11}NO_3$: C, C, 53.49; H, 7.05; N, 8.91. Found: C, 53.42; H, 7.22; N, 8.82.

(*E*)-Ethyl 3-(2-oxopyrrolidin-1-yl)acrylate (24)[14]



24 was obtained following general procedure (Method **A**) as a white crystalline solid (131 mg, 72% yield): mp 118−120 °C; IR (KBr) 3083, 2979, 2905, 1727, 1627, 1460, 1386, 1364, 1326 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 14.4 Hz), 5.28 (d, 1H, *J* = 14.4 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 3.58 (t, 2H, *J* = 7.2 Hz), 2.58 (t, 2H, *J* = 7.2 Hz), 2.22−2.17 (m, 2H), 1.31 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 167.1, 137.2, 100.8, 60.2, 44.9, 30.9, 17.4, 14.3; MS (ESI, +ve) m/z (relative intensity) 206.21 ([M + Na]+, 100%). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.19; H, 7.38; N, 7.72.

(*E*)-Ethyl 3-(3-(4-hydroxyphenyl)-2-oxoimidazolidin-1-yl)acrylate(25)



25 was obtained following general procedure (Method **A**) as a white crystalline solid (99 mg, 54% yield): mp 72−74 °C; IR (KBr) 3402, 2979, 2932, 2901, 1728, 1628, 1480, 1431, 1391, 1368 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J* = 13.6 Hz), 6.03 (bs, 1H), 4.98 (d, 1H, *J* = 13.6 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 3.66 (m, 4H), 1.29 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 157.4, 138.8, 96.3, 59.9, 42.0, 37.4, 14.3; MS (ESI, +ve) m/z (relative intensity) 207.10 ($[M + Na]^+$, 100%). Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.38; H, 6.82; N, 15.49.

3.5 References

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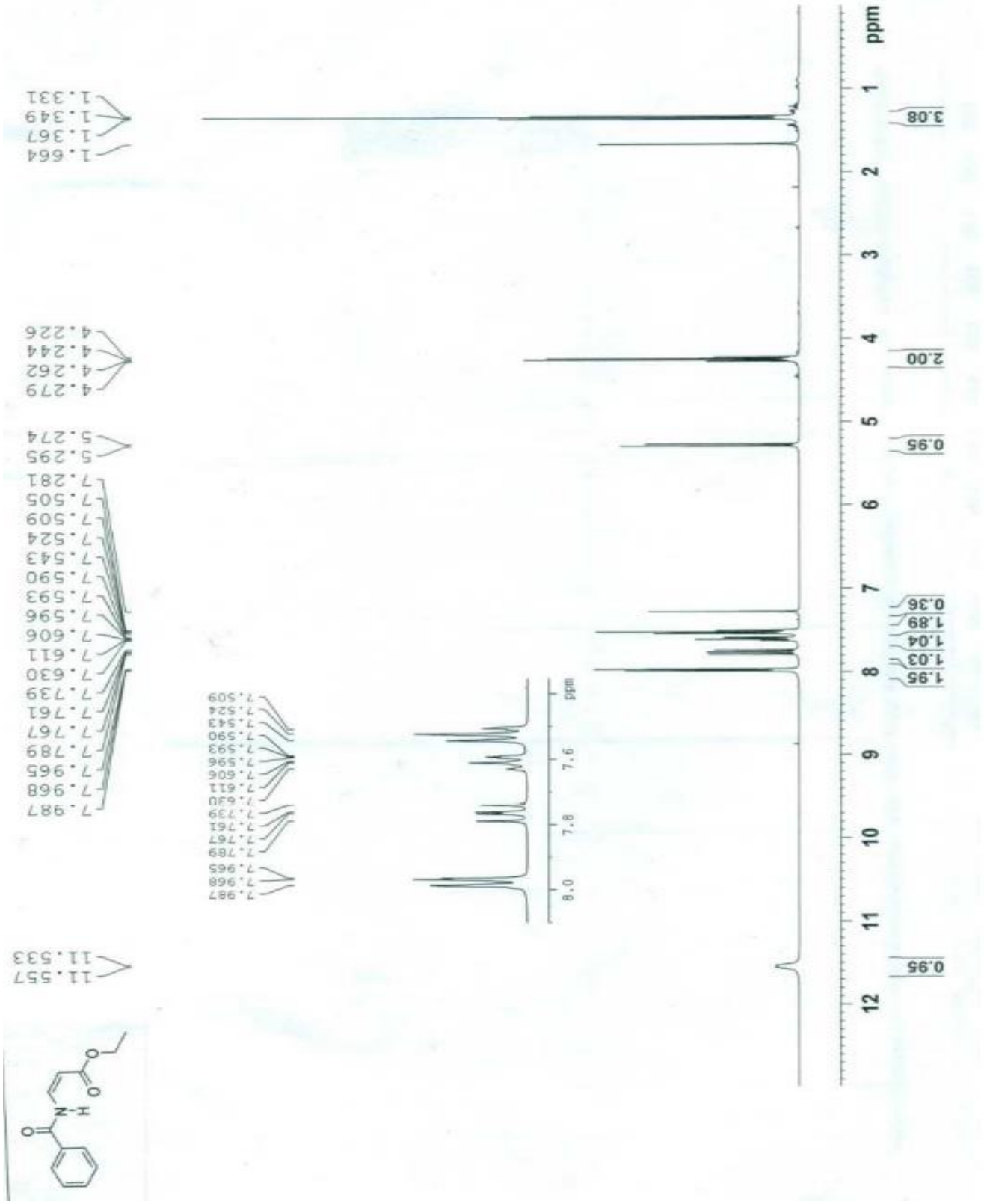
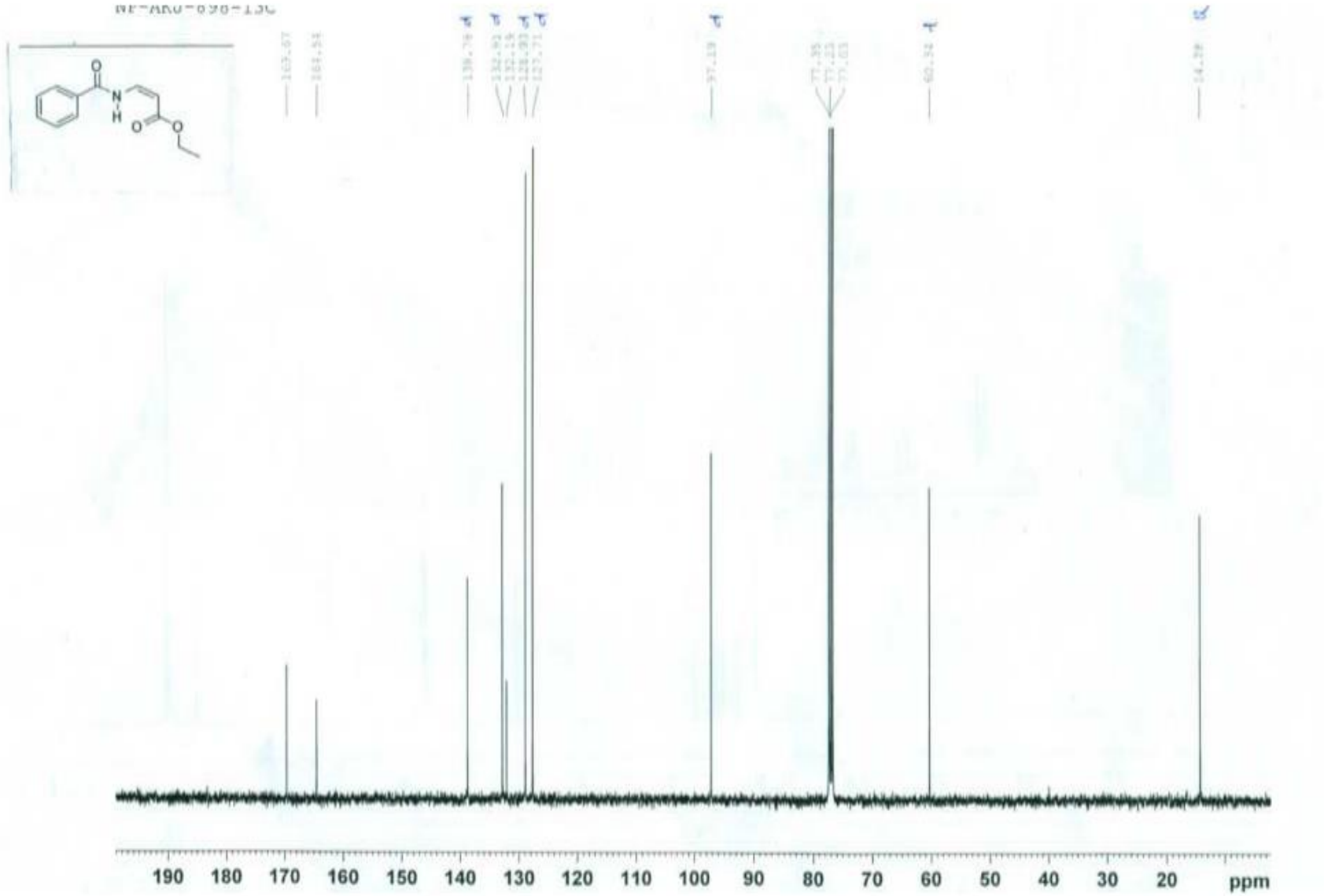
3.6 Selected NMR Spectra

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O
O
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139.79
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132.15
128.90
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97.19
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76.71
60.32
14.29
190
180
170
160
150
140
130
120
110
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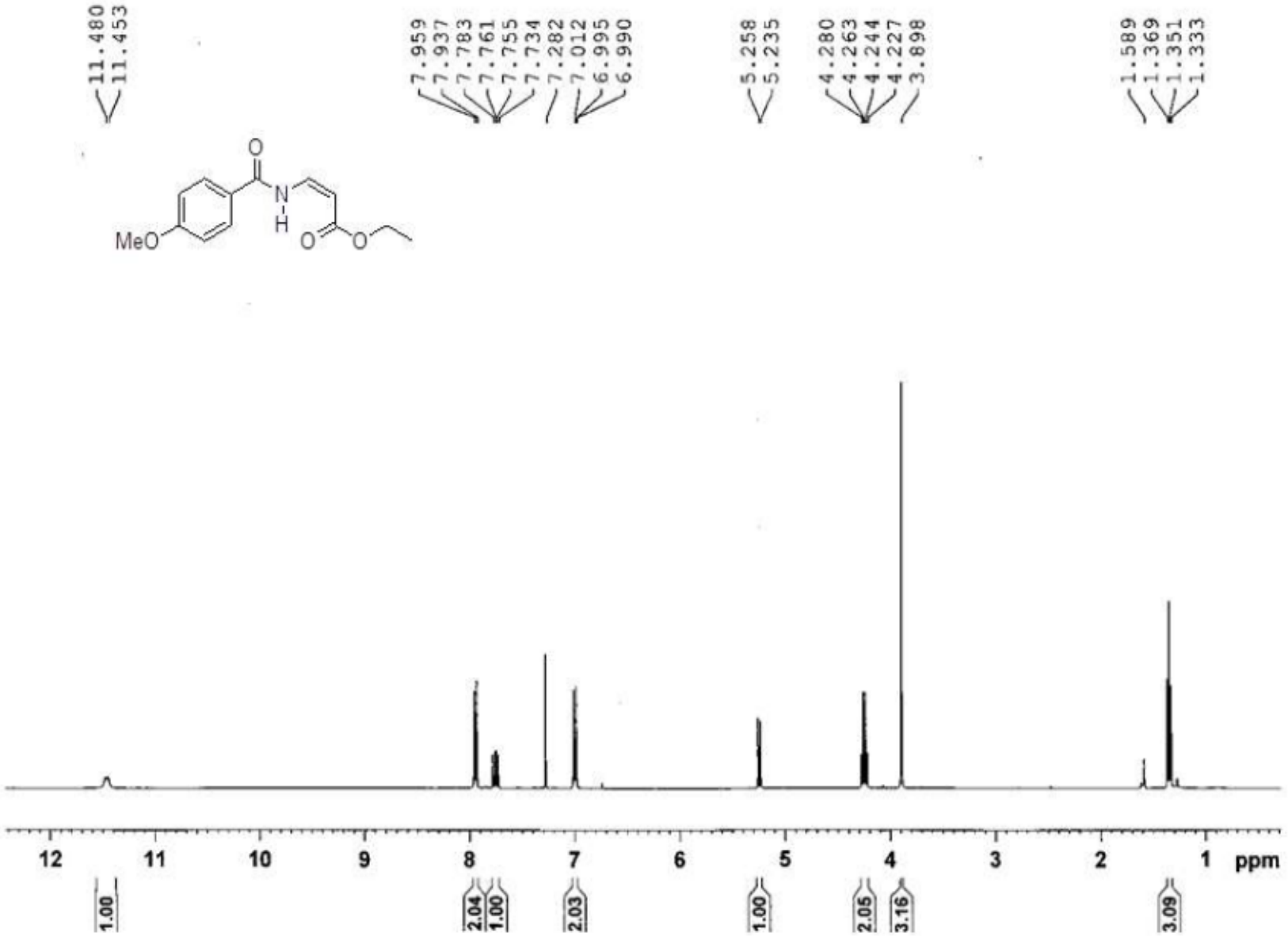
90
80
70
60
50
40
30
20
ppm

NP-MR-433-A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5.258
5.235
4.280
4.263
4.244
4.227
3.898
1.589
1.369
1.351
1.333
MeO
O
N
H
O
O
12
11
10
9
8
7
6
5
4
3
2
1
ppm
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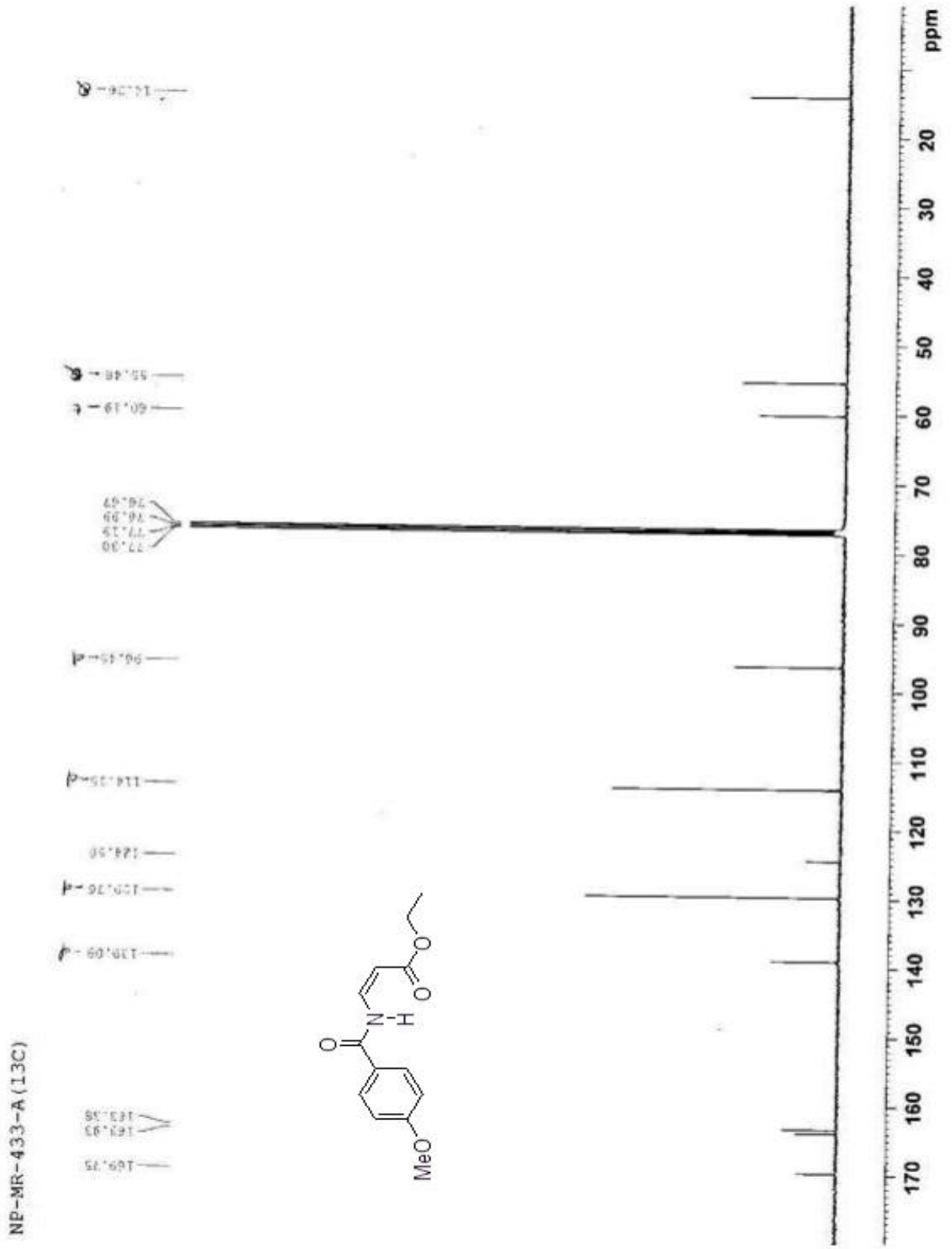
2.04
1.00
2.03
1.00
2.05
3.16
3.09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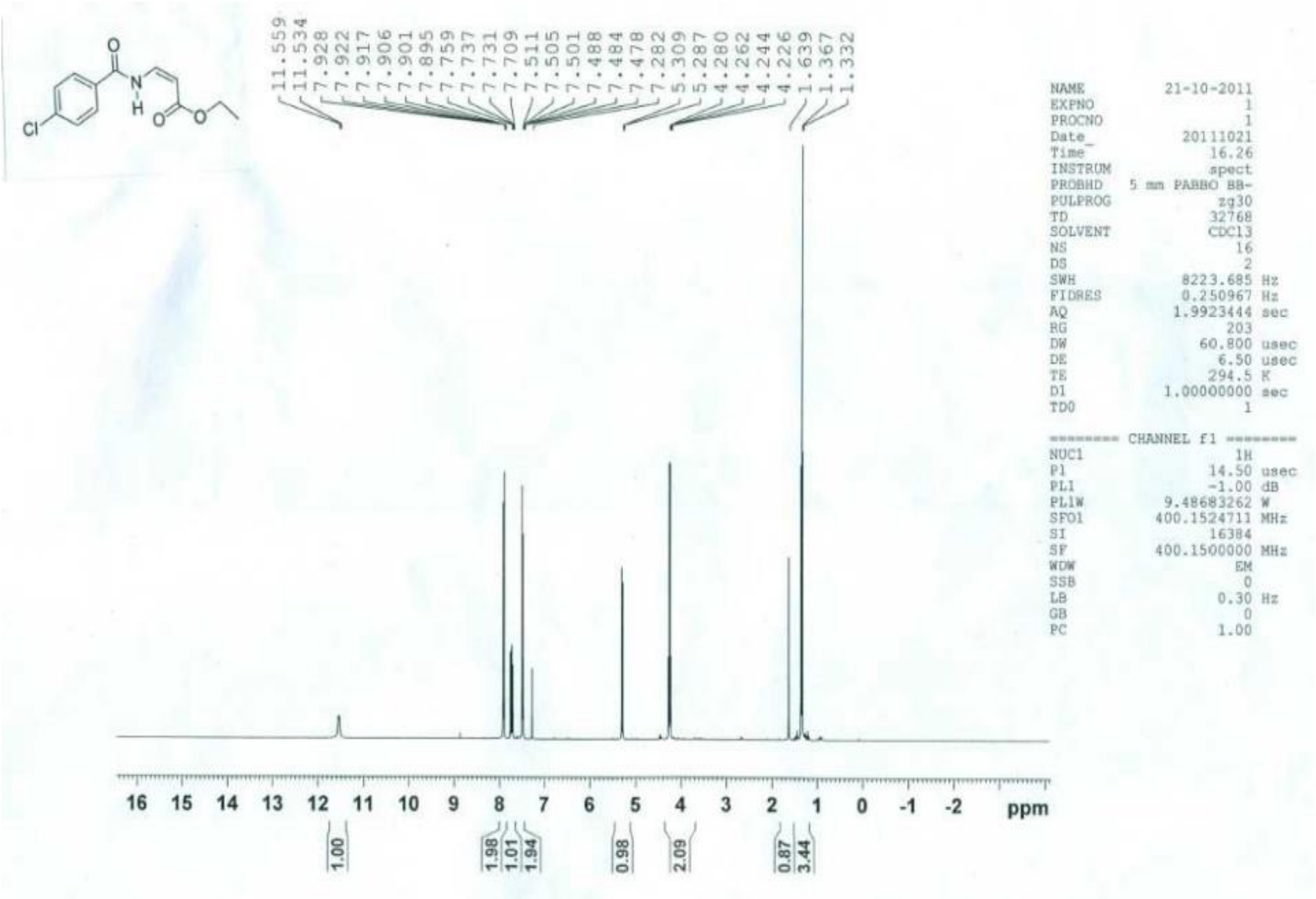
N-H
O
O
O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7.901
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7.759
7.737
7.731
7.709
7.511
7.505
7.501
7.488
7.484
7.478
7.282
5.309
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4.262
4.244
4.226
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1.367
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DE 6.50 usec
TE 294.5 K
D1 1.00000000 sec
TD0 1
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PL1W 9.48683262 W
SFO1 400.1524711 MHz
SI 16384
SF 400.1500000 MHz
WDW EM
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LB 0.30 Hz
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PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
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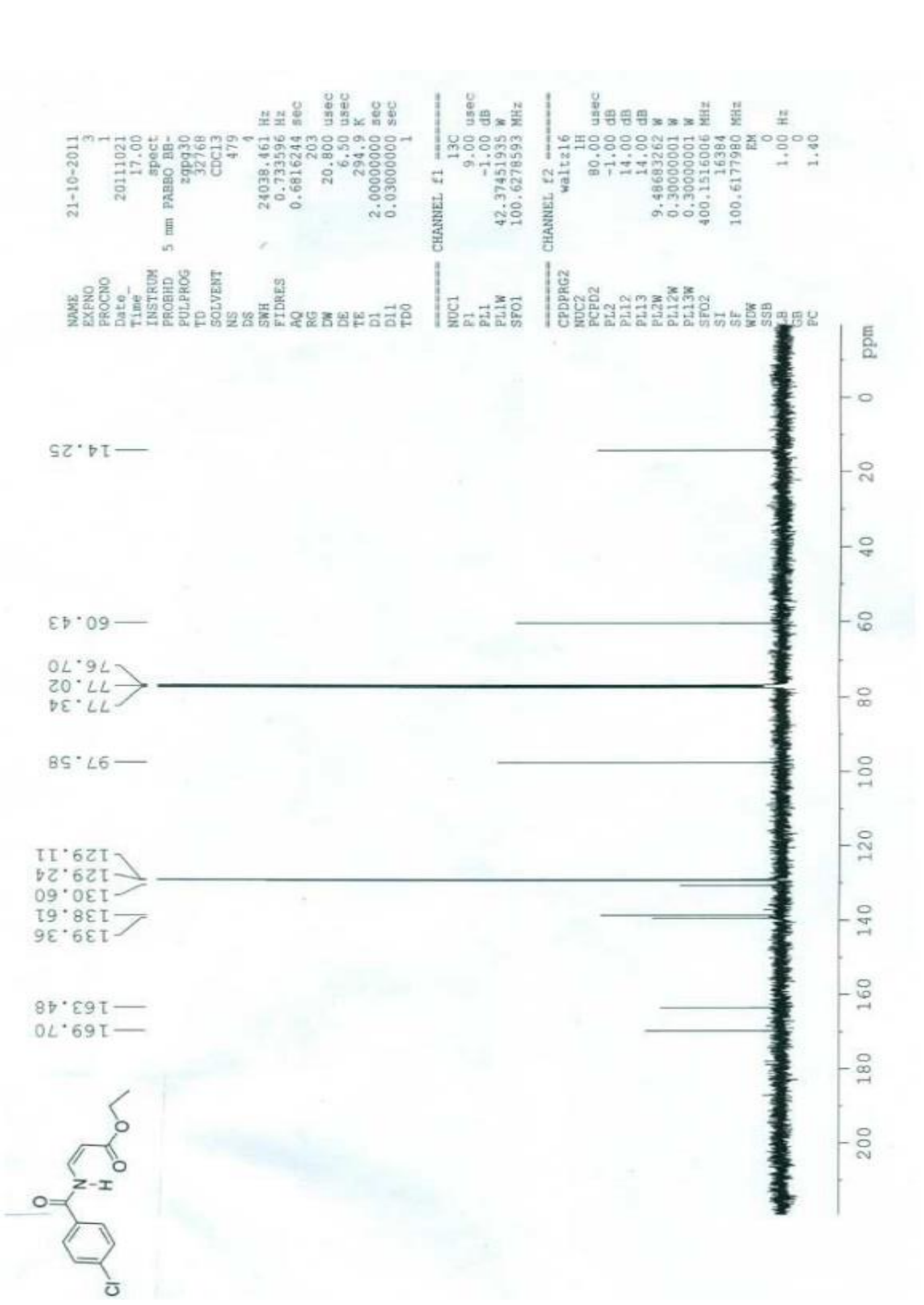
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TD0
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1
20111021
17.00
spect
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zgpg30
32768
CDC13
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4
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0.733596 Hz
0.6816244 sec
203
20.800 usec
6.50 usec
294.9 K
2.00000000 sec
0.03000000 sec
1
CHANNEL f1
13C
9.00 usec
-1.00 dB
42.37451935 W
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CHANNEL f2
waltz16
1H
80.00 usec
-1.00 dB
14.00 dB
14.00 dB
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0.30000001 W
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16384
100.6177980 MHz
EM
0
1.00 Hz
0
1.40
14.25
60.43
76.70
77.02
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129.24
130.60
138.61
139.36
163.48
169.70
ppm
200
180
160
140
120
100
80
60
40
20
0
O
N
H
O
O
Cl

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11.689
8.372
8.368
8.354
8.350
8.345
8.139
8.134
8.121
8.117
7.750
7.728
7.723
7.701
7.281
5.372
5.350
4.284
4.266
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1.347
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2.01
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1.00
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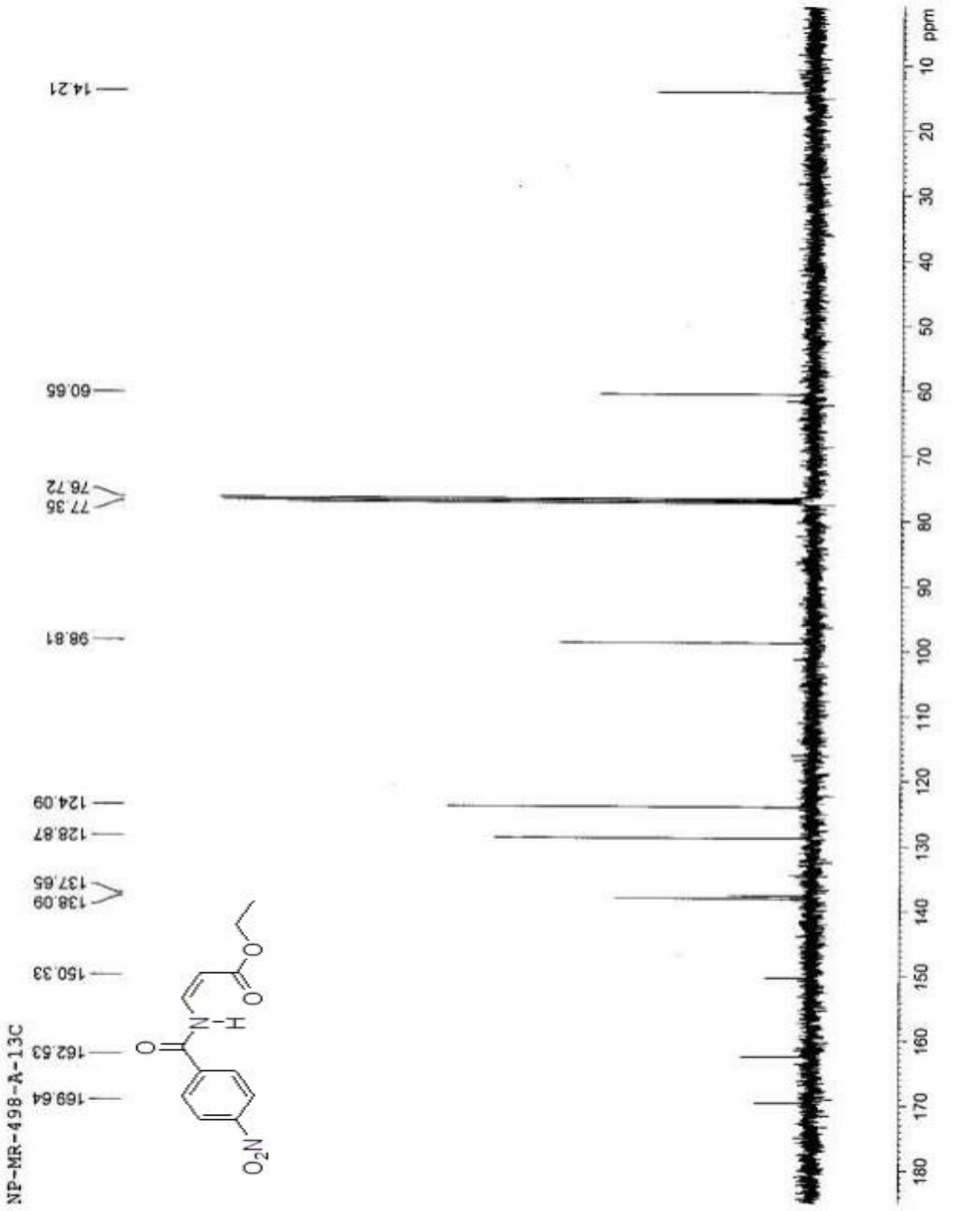
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77.35
76.72
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N
H
O
O
O2N
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

11.305
11.278
7.958
7.939
7.923
7.901
7.895
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7.645
7.627
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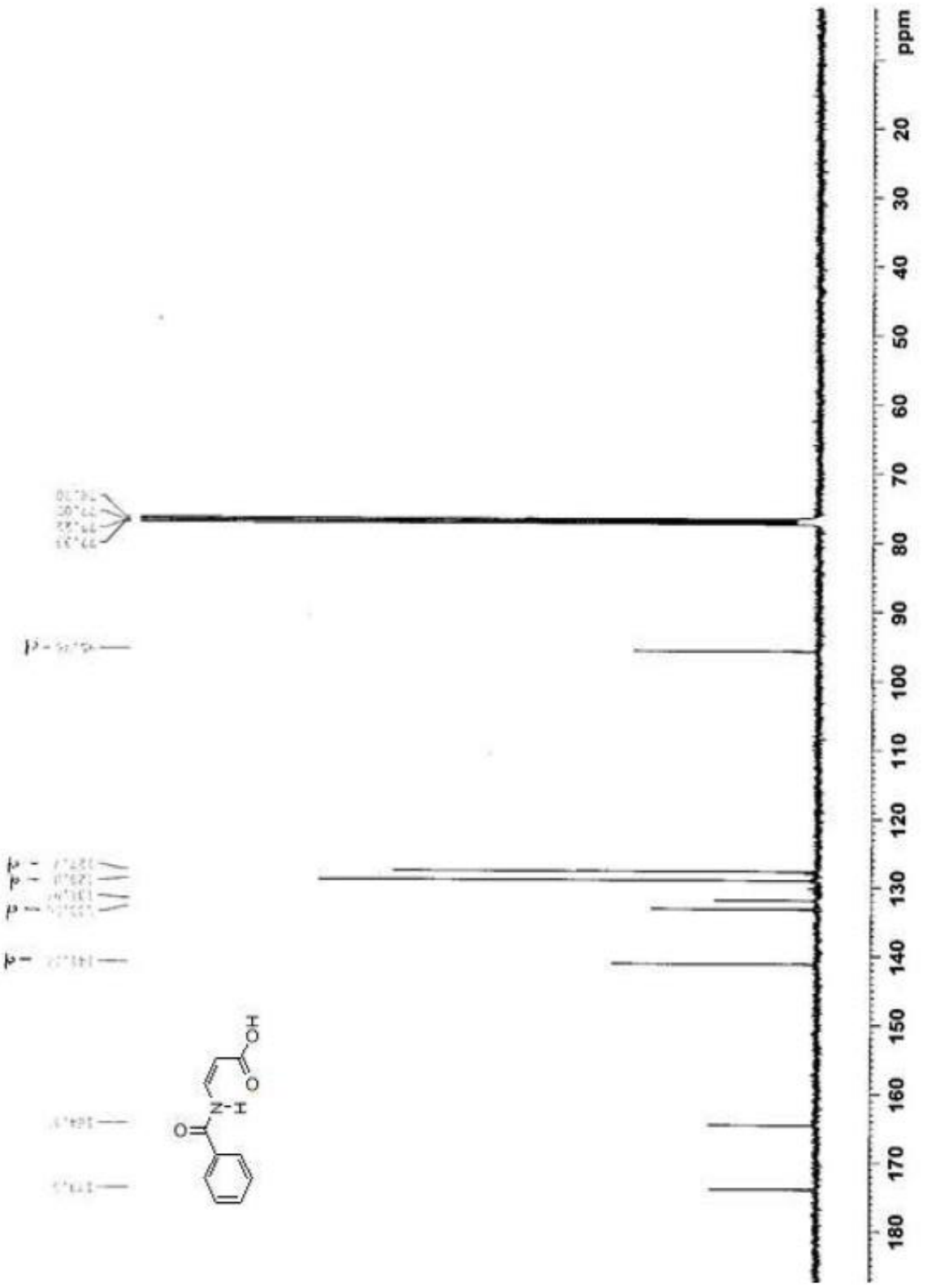
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140
150
160
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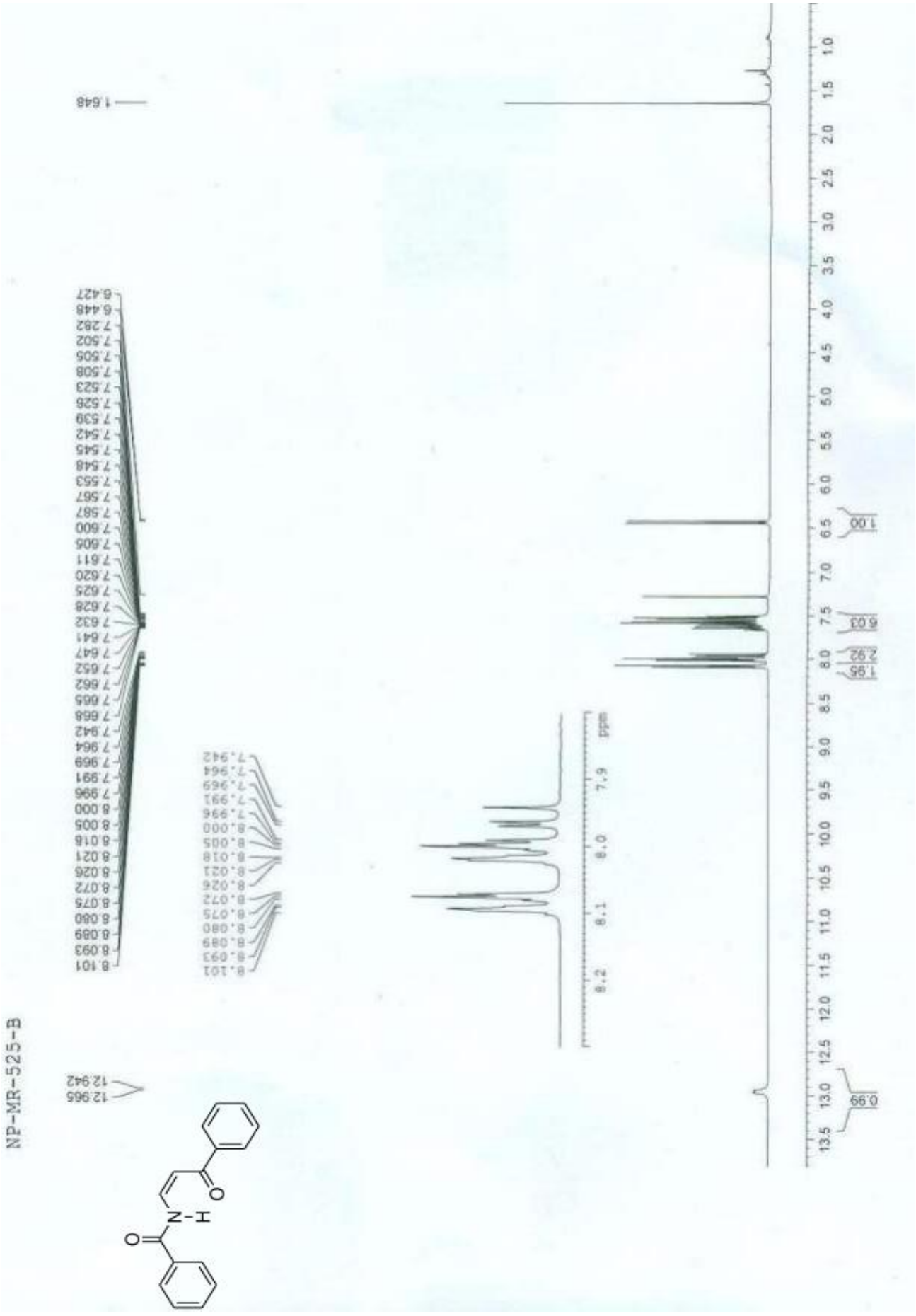
O
H
O
O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8.089
8.080
8.075
8.072
8.026
8.021
8.018
8.005
8.000
7.996
7.991
7.969
7.964
7.942
7.668
7.665
7.662
7.652
7.647
7.641
7.632
7.628
7.625
7.620
7.611
7.605
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7.528
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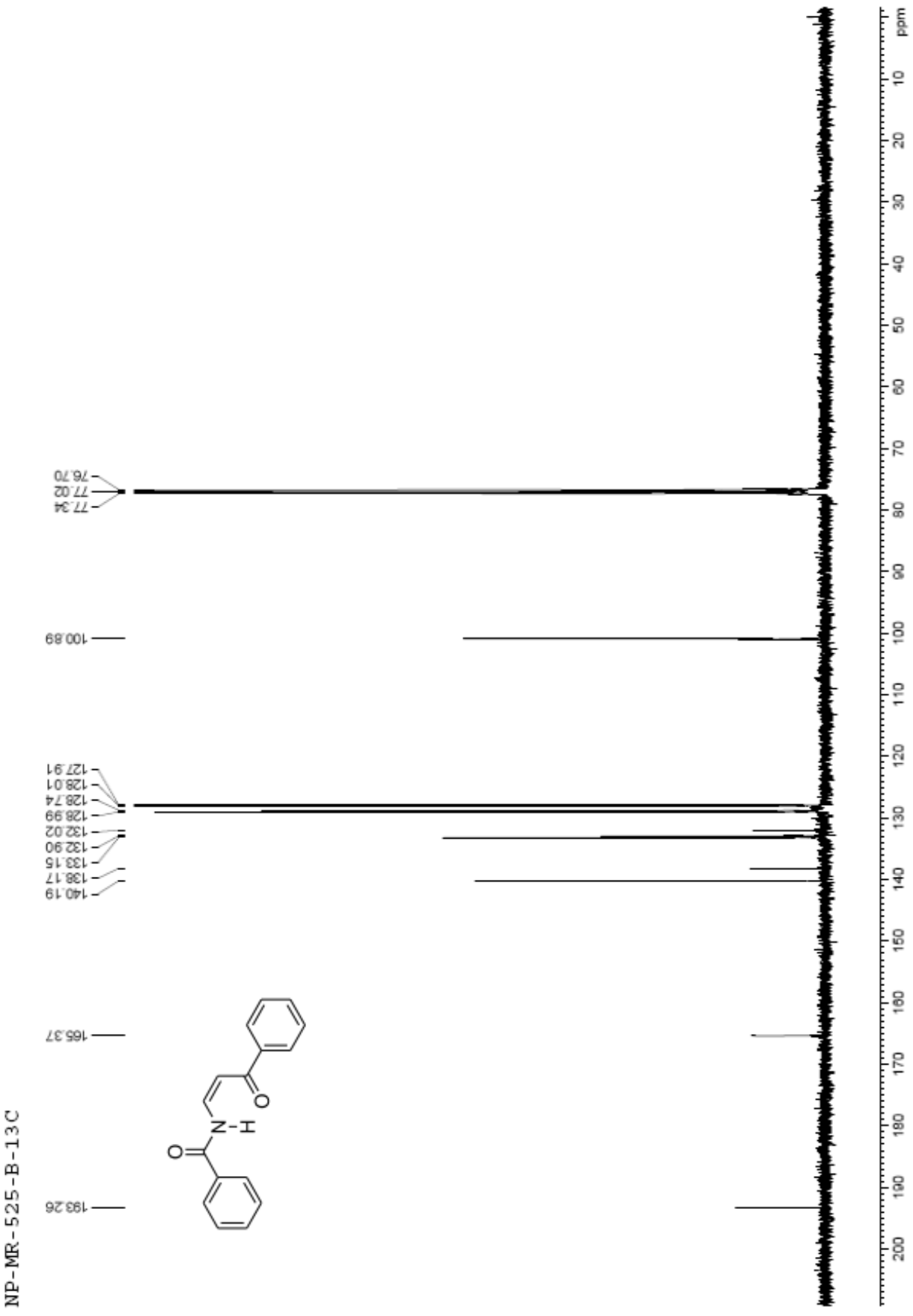
ppm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132.90
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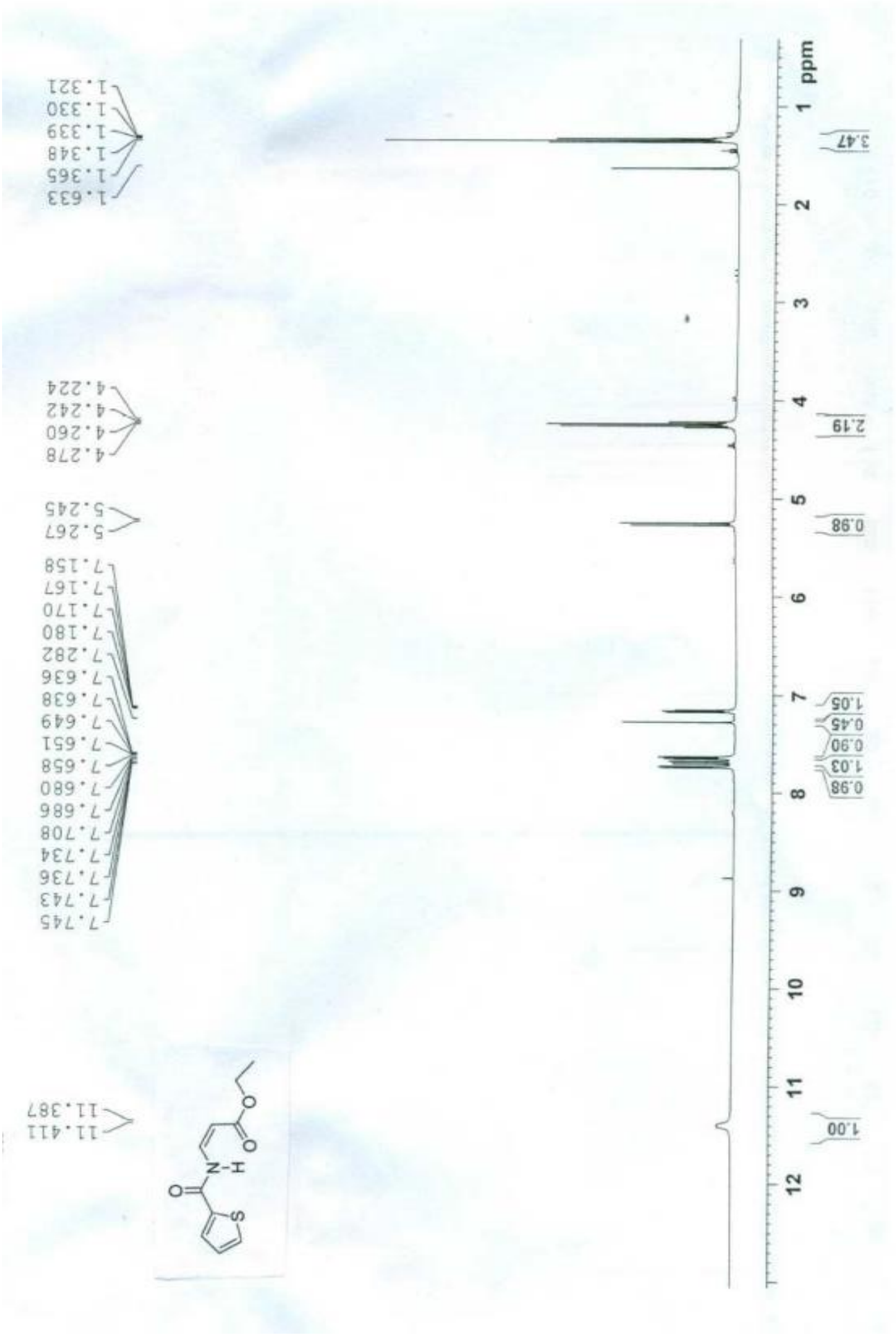
77.02
76.70
O
N-H
O
ppm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7.649
7.638
7.636
7.282
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7.170
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7.158
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5.245
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4.260
4.242
4.224
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1.365
1.348
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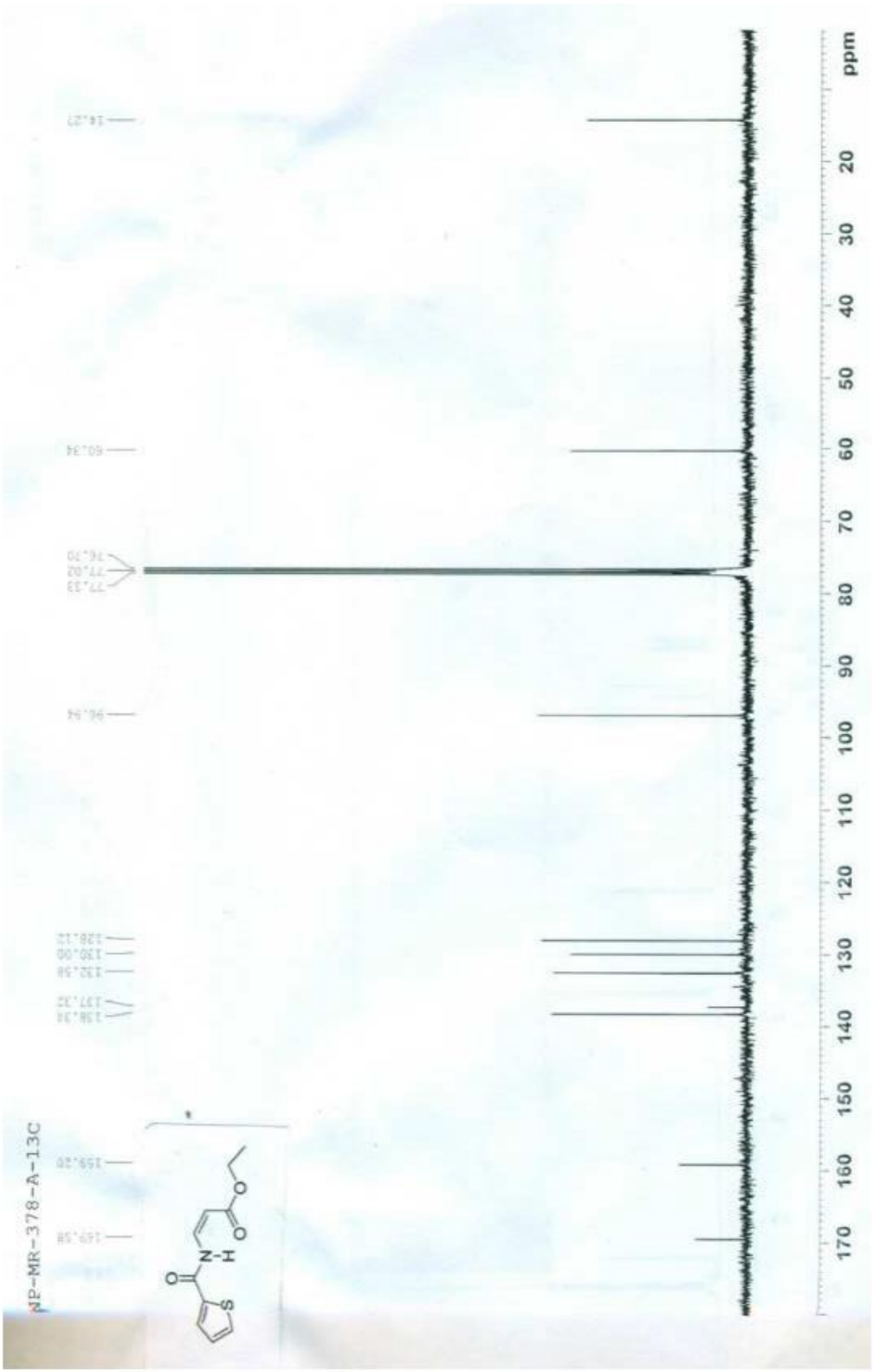
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14.27
ppm
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160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

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7.449
7.443
7.420
5.108
5.086
4.180
4.162
4.144
4.126
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1.286
1.268
1.250
ppm
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3
4
5
6
7
8
9
10
11
3.05
2.98
2.16
0.99
1.00
0.90

14.16
23.53
60.18
76.77
77.09
77.41
96.44
137.86
168.54
169.15
O
N
H
O
O
O
ppm
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40
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60
70
80
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140
150
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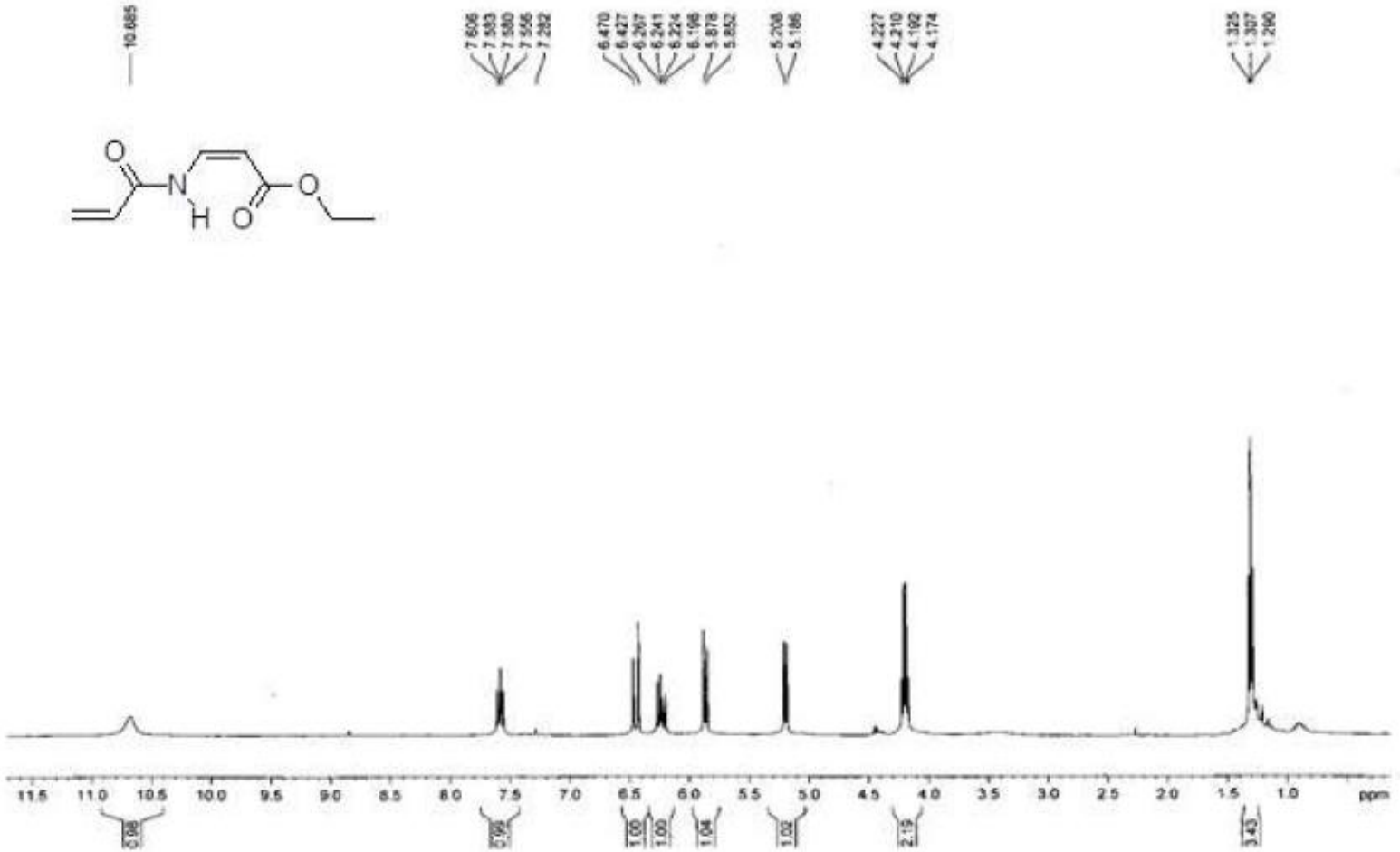
170
180

NP-MR-505-C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5.186
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4.210
4.192
4.174
1.325
1.307
1.290
O
N
H
O
O
11.5
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9.0
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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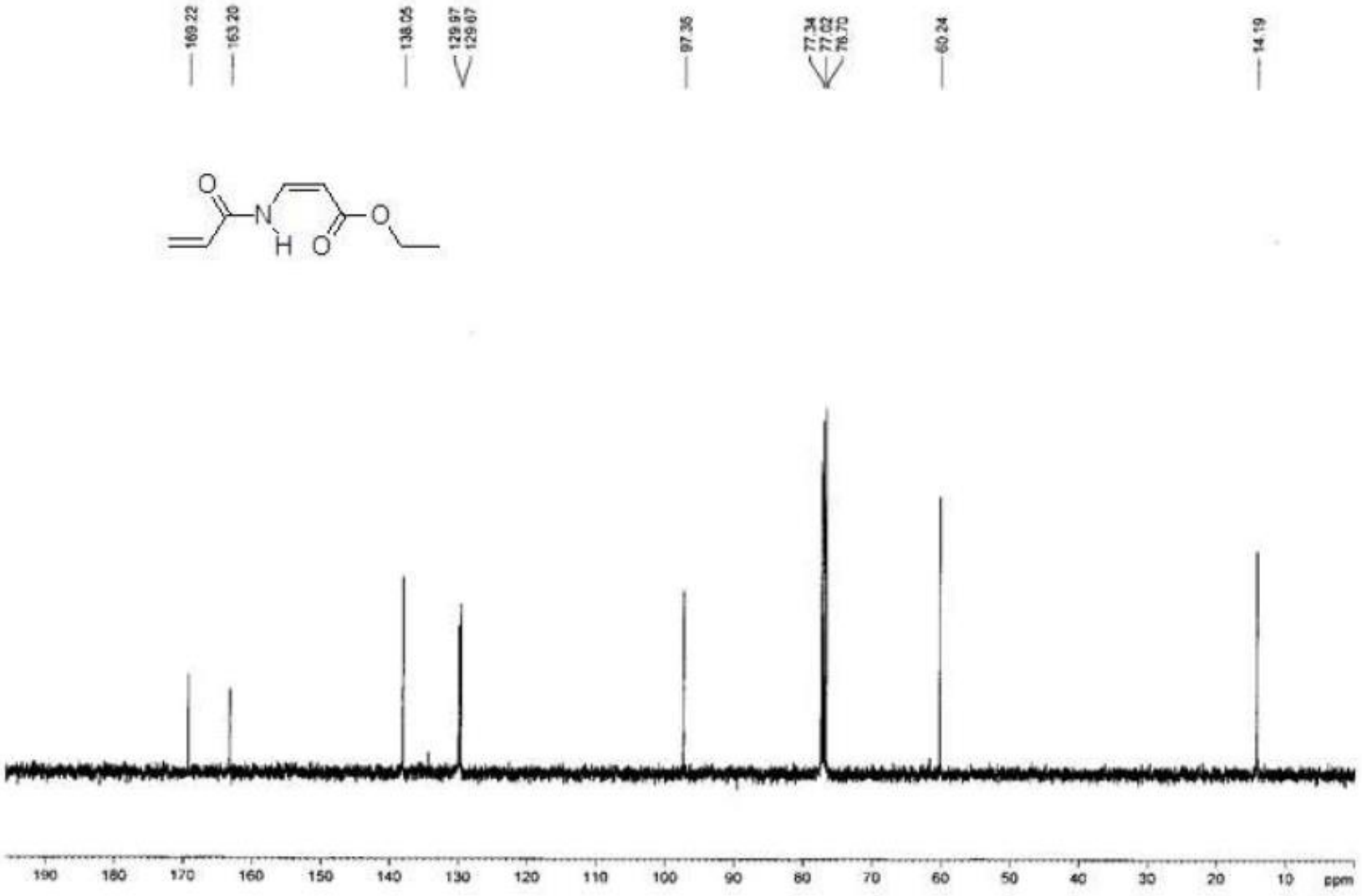

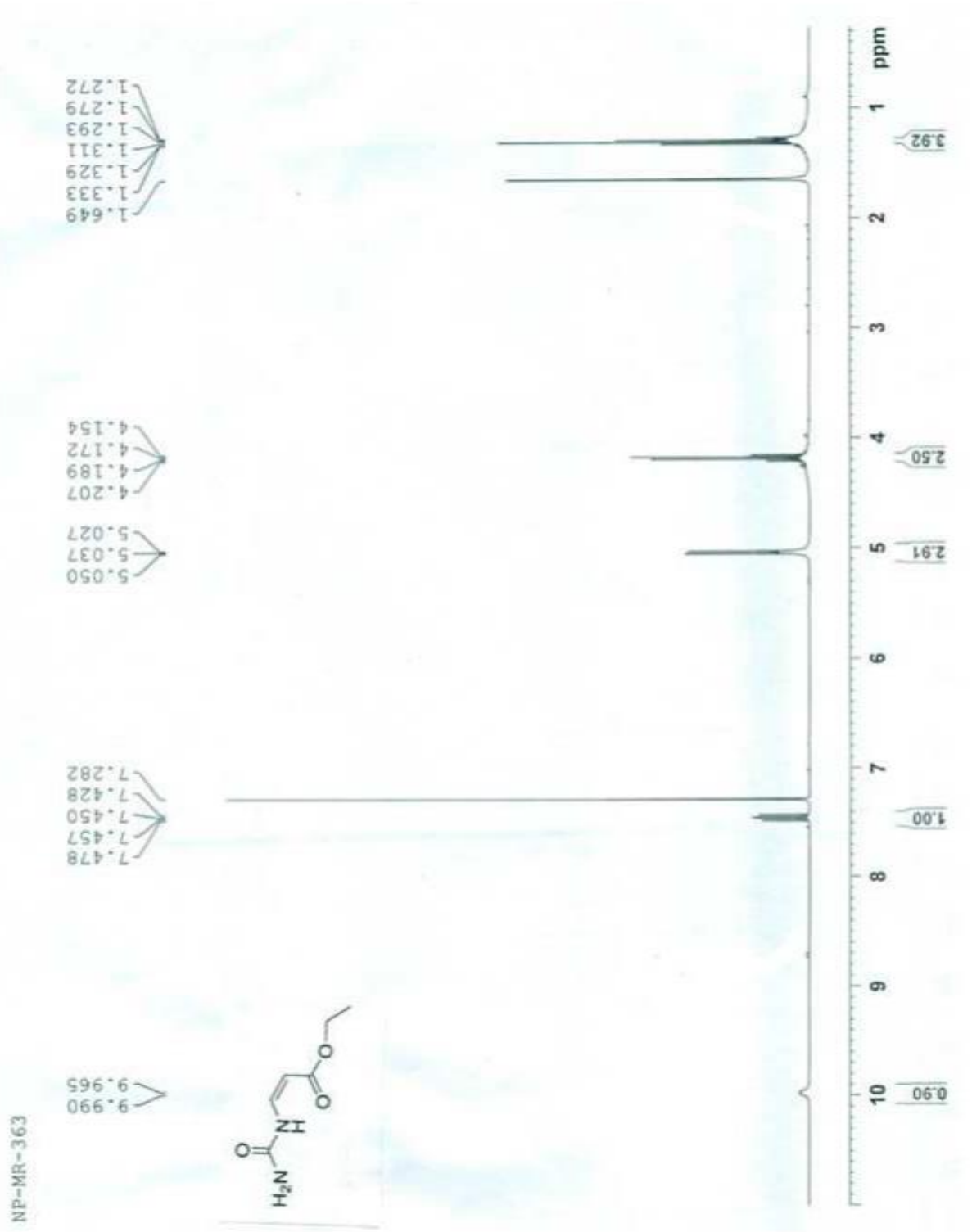
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5.037
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4.189
4.172
4.154
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ppm
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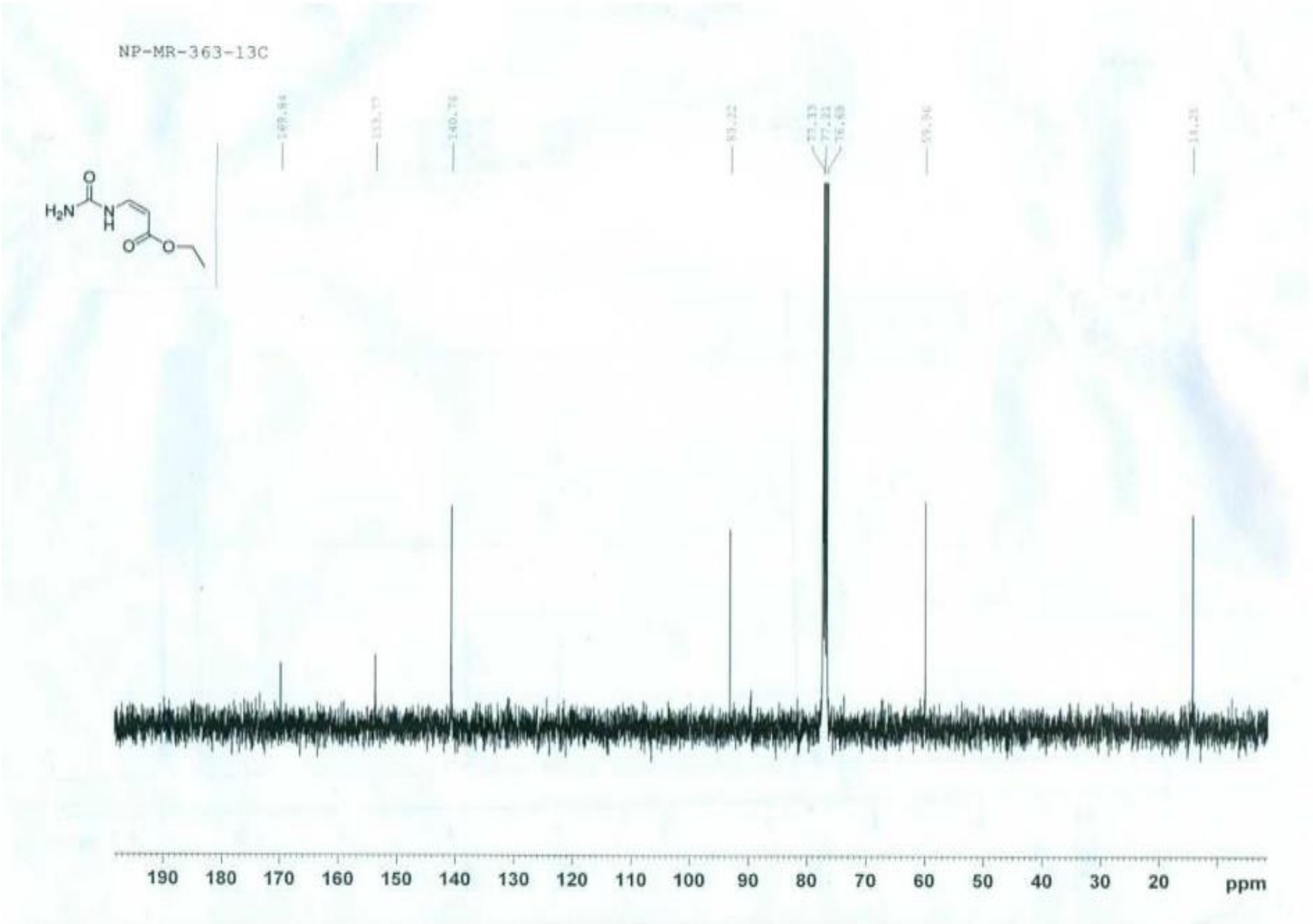
3.92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93.22
77.33
77.01
76.69
59.36
14.25
190
180
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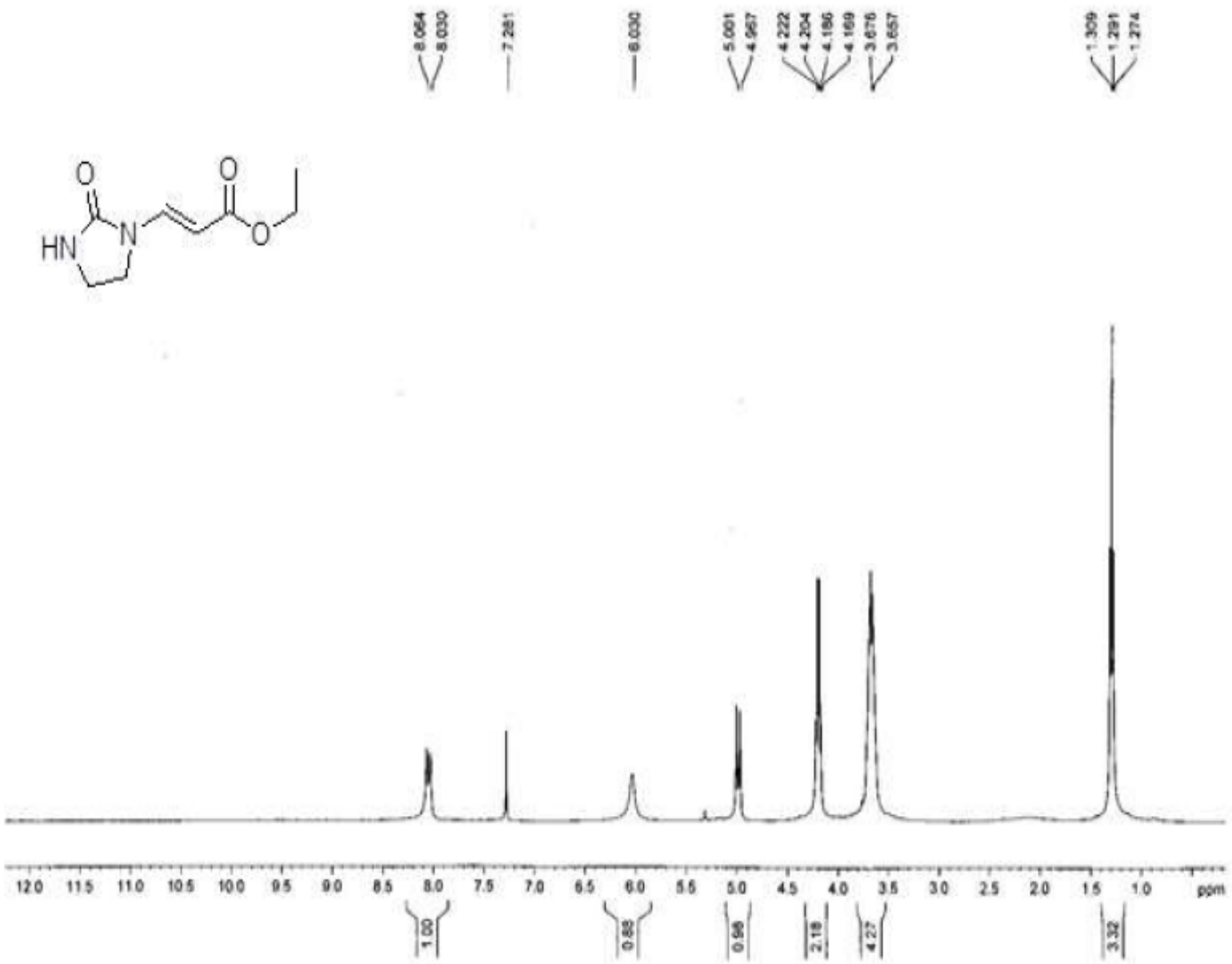
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

NP-MR-500-C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4.204
4.186
4.169
3.676
3.657
1.309
1.291
1.274
O
O
HN
N
O
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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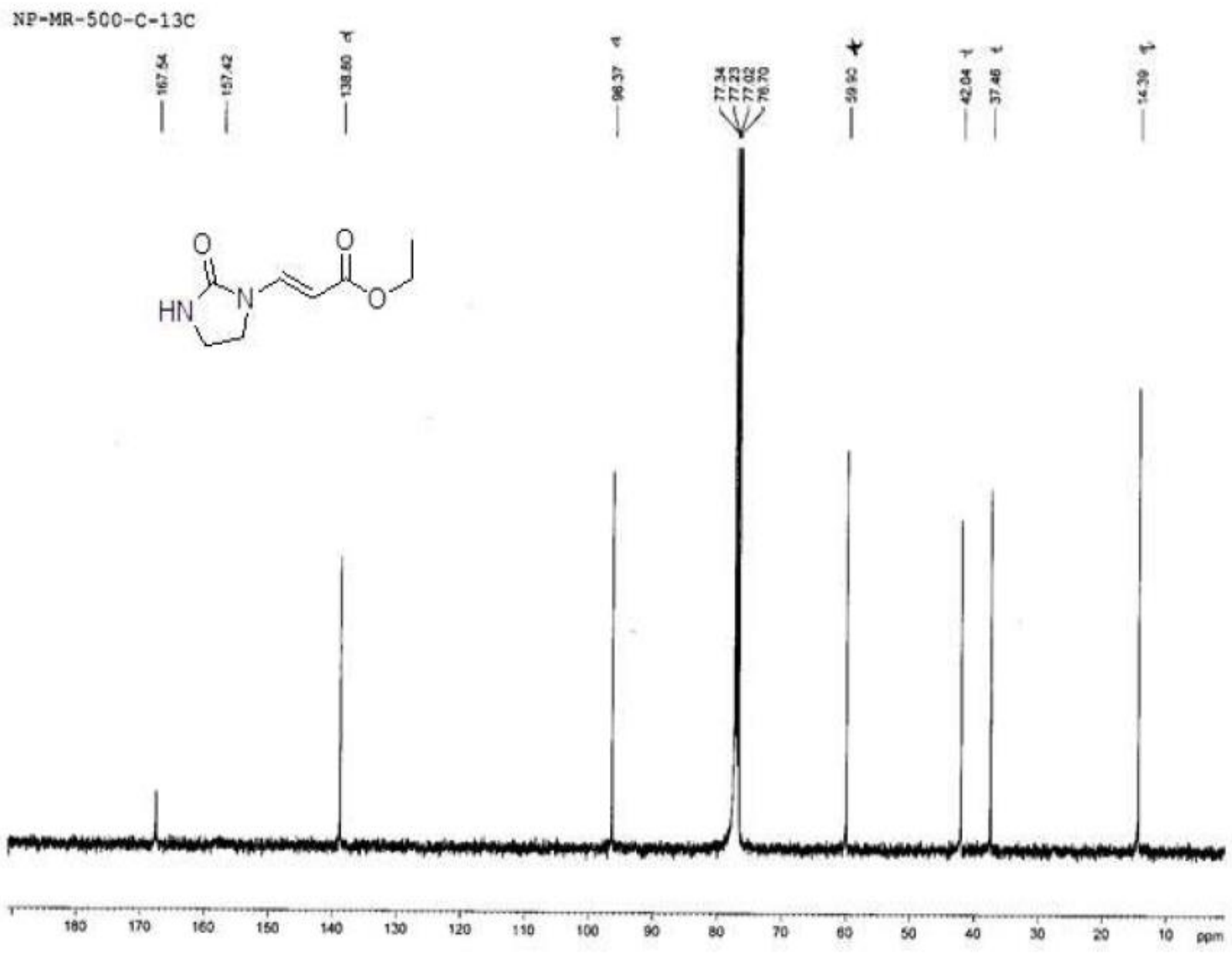
0.98
2.18
4.27
3.32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98.37
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77.23
77.02
76.70
59.92
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14.39
O
O
HN
N
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Chapter 4

Synthesis of Substituted Oxazoles from Enamides

4.1 Introduction

Oxazoles are important precursors in many organic transformations[1] and exist as key structural motifs in many natural products (see Figure **1**).[2,3]They also exhibit a diverse range of pharmacological properties such as antifungal, antiviral, antibacterial, antileukemia, cytotoxic activities, enzyme inhibitory activities and peripheral analgesic activities.[4]Different substitutions to this heterocycle propound a new avenue for drug development and other applications in material science.[5]

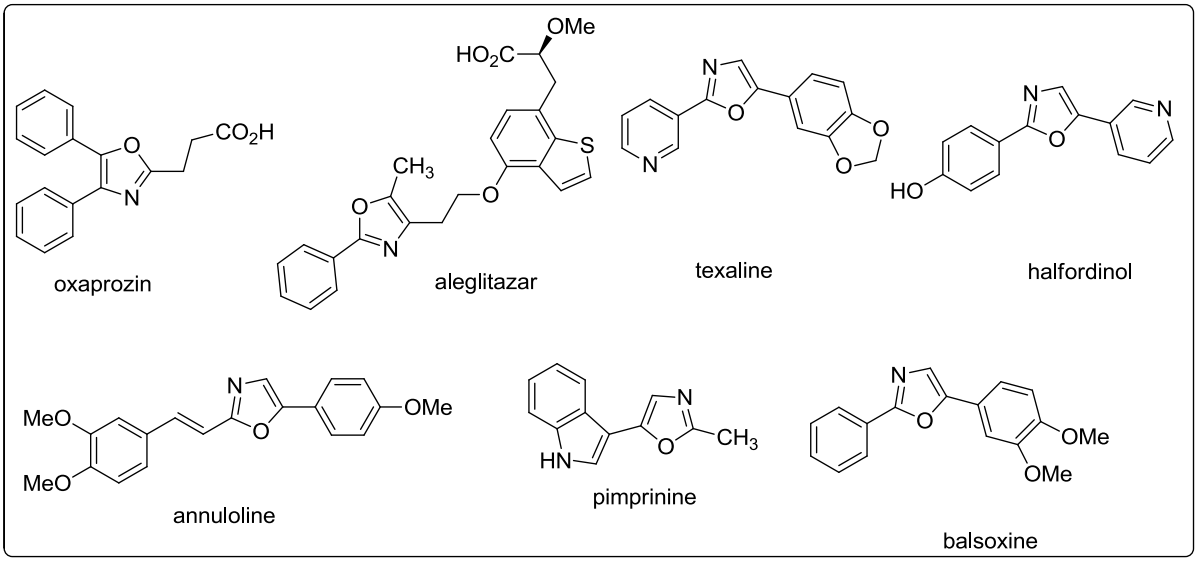


Figure 1: Biologically important oxazoles.

Therefore, impressive synthetic efforts have been made to achieve widely substituted oxazoles. The synthetic routes to oxazoles can be broadly classified as follows:

(i) Intramolecular oxidative cyclization of acyclic precursors to oxazoles, and

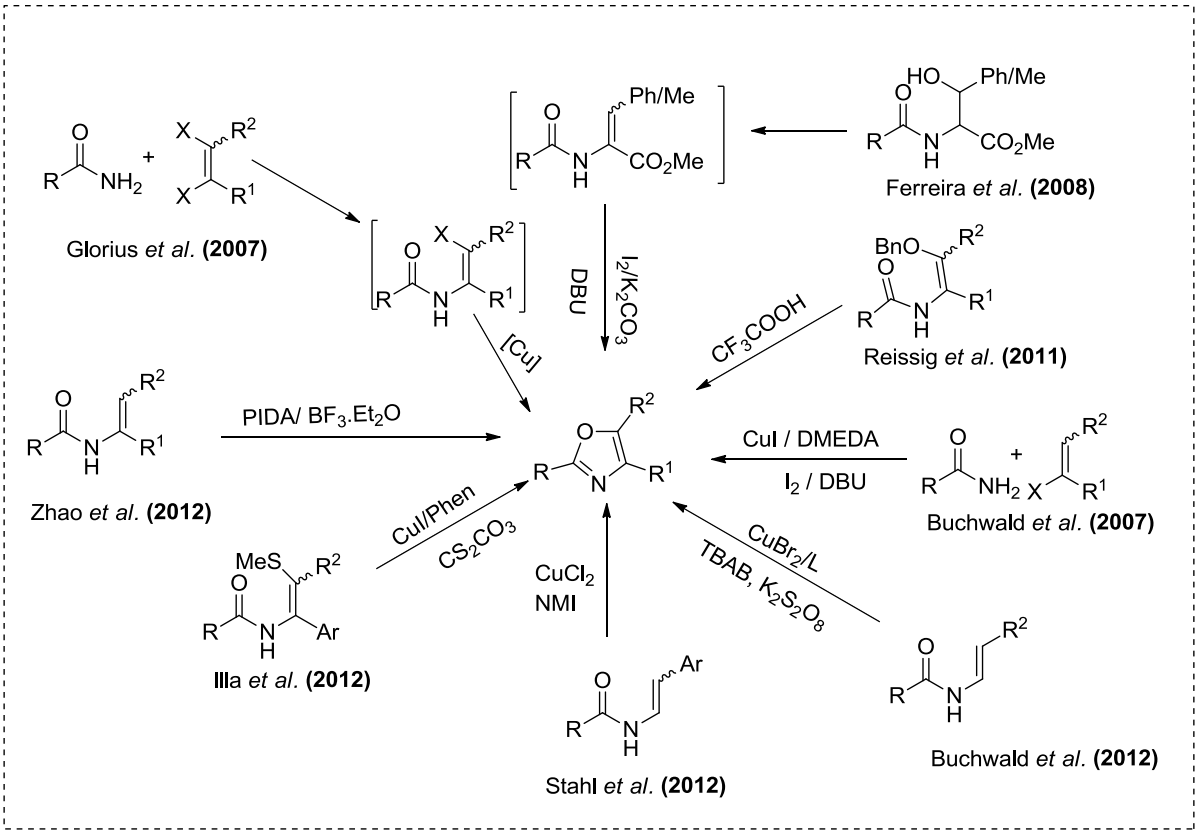
(ii) Transition metal catalyzed functionalization of the oxazole ring to the desired derivatives.

Although the cyclodehydration of 2-acylamino-ketones, esters, or amides in the presence of Lewis or Brønsted acid (known as Robinson–Gabriel condensation) is a classical approach to construct various oxazole skeletons,[6] but the method suffers from drawbacks such as harsh reaction conditions, use of strong Brønsted acid and moderate functional group tolerance.[7]In response to these challenges, several modifications have been continuously documented in recent literature.[8]

Cyclization of enamides has emerged as a potential method to enable the synthesis of a variety of oxazoles. Indeed, enamides with vinylic functionalization undergo base- or acid-mediated cyclization to the corresponding oxazoles (Scheme 1). In this regard, several reports have been disclosed. For instance, Buchwald and his co-workers described the sequential copper-catalyzed amidation of vinyl halides, followed by iodine-promoted cyclization to achieve tri-substituted oxazoles.[9]Glorius and his co-workers have developed the copper-catalyzed preparation of 2,5-disubstituted oxazoles from the reaction of primary amides with 1,2-dihaloalkenes, which was expected to involve a β-haloenamide intermediate.[10]Reissig and his co-workers investigated the acid catalyzed annulation of β-alkoxy-β-ketoenamides into substituted oxazoles[11]Ferreira and his co-workers used a multistep process to synthesize 2,4,5-substituted oxazoles from amino acid derivatives.[12] In a recent report, Wendlandt and Stahl reported the $CuCl_2$/NMI (2 equiv.each)-mediated intramolecular cyclization of enamides (without vinylic C–H functionalization) at 140 ºC.[13]

Later, Cheung and Buchwald demonstrated the $CuBr_2$/ethyl nicotinate-catalyzed oxidative cyclization of enamides to synthetically difficult 2,5-substituted oxazoles via vinylic C–H bond functionalization.[7] Du and Zhao prepared substituted oxazoles by the phenyliodine diacetate (PIDA)-mediated intramolecular cyclization of enamides in the presence of BF_3 Et_2O. It may be mentioned here that although this method is suitable to achieve a series of 2,4,5-trisubstituted oxazoles, its scope was less extended to produce 2,5-disubstitituted oxazoles.[14] H. Ila and her co-workers used thio-substituted enamides for cyclization to form the corresponding oxazoles in the presence of copper iodide and 1,10-phenanthroline.[15]Very recently, Bathula and his co-worker described the NBS-mediated synthesis of substituted oxazoles from *N*-acylated amino acid derivatives through an iterative bromination and debromination process from amino acid derivatives. It was proposed that the reaction proceeded via enamide intermediate.[16]

In regard to these useful methods it may be envisaged that the depicted transformations are mostly substrate specific (leading to either 2,5-or 2,4,5-substitituted oxazoles) and/or associated with intricacy in the generation of selective starting materials (i.e. β-halo or β-mercapto or β-benzyloxy enamides) to produce either 2,5 or 2,4,5-substituted oxazoles. Moreover, employment of a single method to produce both 2,5 or 2,4,5-substituted oxazoles is less literature precedent. Consequently, the increasing demand of functionalized oxazoles indeed garners interest for an efficient and practical method for their preparation.



Scheme 1. Reported synthesis of 2,5 and 2,4,5-substituted oxazoles by cyclization of enamides/preformed enamides.

In continuation of our work on enamide synthesis, we here in disclose a metal-free, practical approach to generating 2,5- and 2,4,5-substituted oxazoles from easily accessible enamides in one-pot under mild reaction conditions. Our strategy involves the use of NBS–Me_2S (Corey–Kim reagent)-mediated intramolecular cyclization of substituted enamides in the presence of mild base to produce desired oxazoles.

4.2 Results and Discussion

In the past few years, we have developed the Pd-catalyzed amidation of electron deficient alkenes[17] and alkynes[18] to generate *Z*-enamides. Possible intramolecular hydrogen bonding between the amido N–H proton and carbonyl oxygen in the intermediate might be responsible for *Z*- selectivity of the reaction. Since synthetically difficult 2,5 oxazoles are the key structural motifs in many natural products as well as pharmaceuticals,[9] direct synthesis of substituted oxazoles from our enamides deemed to be important. Moreover, intramolecular cyclization of such electron deficient enamides to required oxazoles has less literature precedent; that stimulates us to develop a suitable protocol to access such oxazoles. We started our investigation with the intramolecular cyclization of enamide (**1**) to the

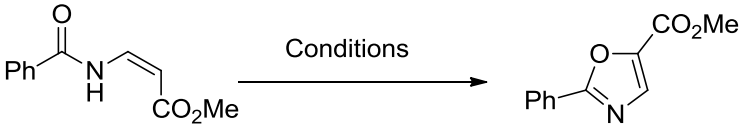
corresponding oxazole (**2**) following the analogous procedure reported by Ferreira and his co-worker.[19]Thus, when enamide **1** was treated with I_2/K_2CO_3/DBU in THF at 80 ºC (Table 1, entry 1), surprisingly oxazole **2** was not produced rather enamide **1** was isomerized to thermodynamically more stable *E*-enamide exclusively. The reaction of enamide **1** in the presence of 3 equiv. of NBS in DCE at 100 ºC did not result in oxazole (**2**); rather β-bromoenamide was produced (Table 1, entry 3).[16] Furthermore, following the similar reaction conditions reported by Yoshimura,[20] when enamide **1** was heated with NBS and triethyl amine in benzene under reflux condition, no reaction took place, albeit cis–trans isomerized enamide was isolated (Table 1, entry 4). An attempt to acid catalyzed annulations of enamide **1** to oxazole **2** by employing the similar procedure reported by Reissig was found to be unsuccessful.[11]

This failure persuaded us to modify the reaction conditions to prepare 2,5-substituted oxazoles. After several experimentations, we observed that the solvent plays a vital role in the cyclization process. For instance, when, enamide **1** was treated with I_2 in the presence of a base in a non-polar solvent such as toluene, only β-iodoenamide was obtained (Table 1, entry 2). This may be due to the poor solubility of the base in toluene. However, when a mixture of solvents such as toluene and DMF (3:1) was taken to improve the solubility of the base and reagents 2,5-disubstituted oxazole was achieved in 33% yield (Table 1, entry 5).

Formation of oxazole **2** was evident from NMR Spectroscopy, Mass spectrometry and IR Spectroscopy. The ^{1}H NMR spectrum contains singlet at δ 7.87 corresponding to the =C-H in oxazole moiety and 9 line signals in ^{13}C NMR spectrum confirmed the structure of oxazole. A sharp peak at 1712 cm $^{-1}$ in IR spectrum provides evidence for the presence of ester group. Molecular ion peak at 204.06 ($[M + H]^+$, 100%) further confirmed the formation of oxazole **2**.

Replacing the oxidant I_2 with *N*-bromo succinimide (NBS) results in a negligible yield of **2** (Table 1, entry 9).However, addition of dimethylsulfide along with NBS (Corey–Kim reagent) to the reaction mixture in the presence of mild base such as K_2CO_3 at 70 ºC improves the yield of oxazole **2** substantially (79%)(Table 1, entry 10). Further screening of bases such as ^{t}BuOK, Cs_2CO_3, KOH, Et_3N and DBU did not lead to better yield of oxazole (Table 1, entries 19–22). It may be noted that, under controlled reaction conditions, when 1 was treated with NBS–Me_2S in the absence of base, a mixture of cis–trans β-bromoenamides (from NMR) was obtained (Table 1, entry 23).

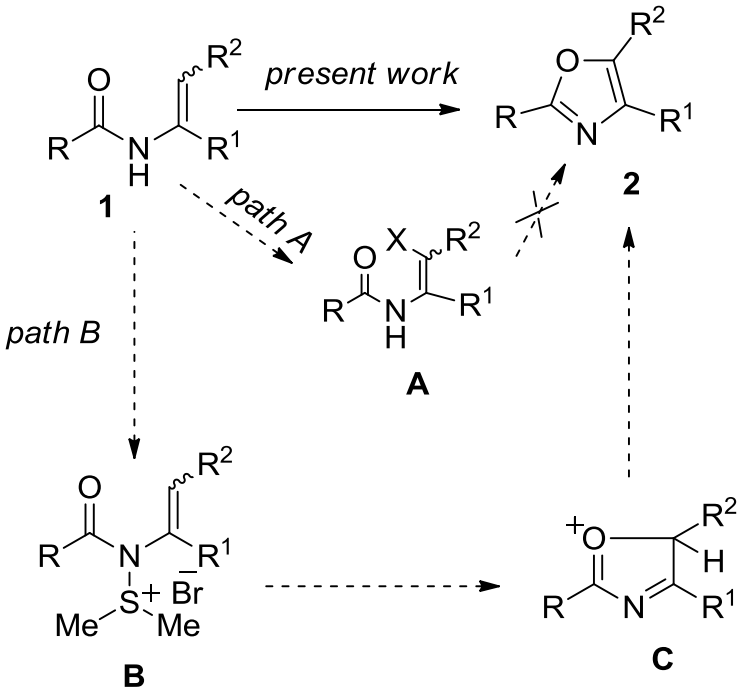
Table 1.Optimization of reaction conditions [a]



Entry	Oxidant	Base	Additive	Solvent	(2a)
1[b]	I_2	K_2CO_3/DBU	—	THF	0
2[c]	I_2	K_2CO_3	—	Toluene	0
3[c]	NBS	—	—	DCE	0
4	NBS	Et_3N	—	Benzene	NR
5	I_2	K_2CO_3	—	Toluene/DMF	33
6	Br_2	K_2CO_3	—	Toluene/DMF	12
7	ICl	K_2CO_3	—	Toluene/DMF	NR
8	Chloramine-T	K_2CO_3	—	Toluene/DMF	NR
9	NBS	K_2CO_3	—	Toluene/DMF	10
10	**NBS**	**K_2CO_3**	**Me_2S**	**Toluene/DMF**	**79**
11	NBS	K_2CO_3	Me_2S	Toluene	17
12[b]	NBS	K_2CO_3	Me_2S	DMF	0
13[b]	NBS	K_2CO_3	Me_2S	DMSO	0
14[b]	NBS	K_2CO_3	Me_2S	THF	0
15	NBS	K_2CO_3	Me_2S	H_2O	0
16[c]	NBS	K_2CO_3	Me_2S	Toluene/H_2O	0
17	NBS	K_2CO_3	Me_2S	Toluene/DMF	NR
18	NBS	K_2CO_3	Me_2S	Toluene/DMSO	22
19	NBS	KOH	Me_2S	Toluene/DMF	37
20	NBS	^tBuOK	Me_2S	Toluene/DMF	0
21	NBS	Et_3N	Me_2S	Toluene/DMF	0
22	NBS	DBU	Me_2S	Toluene/DMF	0
23[c]	NBS	—	Me_2S	Toluene/DMF	0
24	NBS	K_2CO_3	Me_2S	DCE	NR

Reaction conditions: a) mixture of enamide (100 mg), oxidant (1.2 equiv.), and additive (0.1 mL), in solvent (4 mL) was heated at 70 ºC for overnight. b) Mixture of *E* and *Z*-enamides (3) forms. c) β-Haloenamide forms. NR: no reaction.

Undesirably, treatment of isolated β-bromoenamides (**A**) with K_2CO_3 at 70 ºC did not produce the expected oxazole with the complete recovery of the starting material i.e. β-bromoenamide. Thus, we speculate that under our mild reaction conditions, intermediate **B** may form, which subsequently undergo facile intramolecular reaction leading to the intermediate **C** (Scheme 2). Aromatization of the intermediate **C** produces the desired oxazole **2**. Among the tested solvents combination of toluene and DMF (3:1) turned out to be the best solvent for the annulation reaction and hence it was selected as the solvent in the following tests. Furthermore, it may be mentioned here that when *E*-enamide was taken as a reactant, oxazole **2** was isolated with similar yield; which indicates that the stereochemistry of enamide does not affect the yield of oxazole. With the optimized reaction conditions, we turned our attention to investigate the substrate scope of the annulation reaction

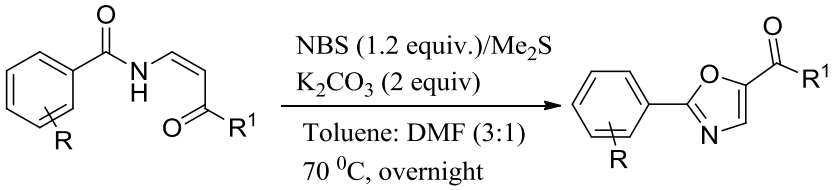


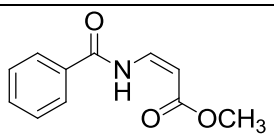
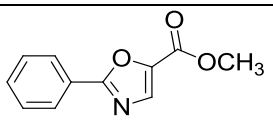
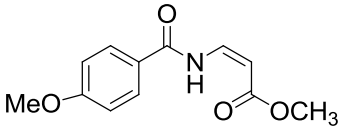
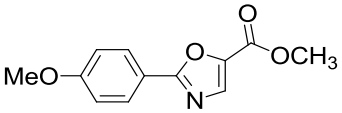
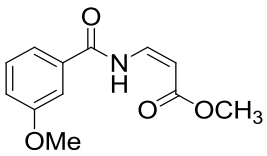
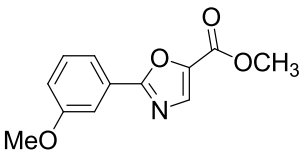
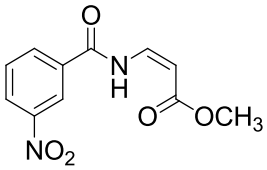
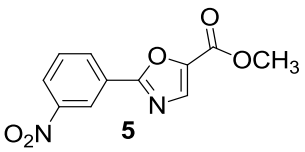
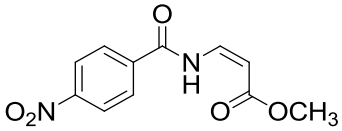
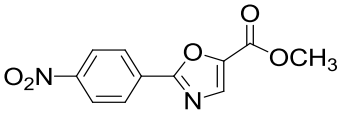
Scheme 2. The present approach to oxazoles from enamide.

We observed that under our optimized reaction conditions, substrates with electron-donating or -withdrawing substituents to the aromatic ring were successfully transformed to 2,5-substituted oxazoles in one-pot with good to excellent yield (Table 2). Heteroaromatic enamides also afford the heteroaryl substituted oxazoles in good yield. 2,5-disubstituted thioxazole (17) was also obtained from the cyclization of the corresponding thioenamide in appreciable yield (Table 2, entry 16). Unfortunately, however, the reaction did not afford the corresponding oxazole when we use *N*-styrylbenzamides, which indicates that the presence of

an electron withdrawing group at the β-position in the enamide is indispensible for the reaction to occur.

Table 2. Synthesis of 2,5-disubstituted oxazoles



Entry	Enamide	Oxazole	Yield(%)
1		 **2**	79
2		 **3**	76
3		 **4**	81
4		 **5**	80
5		 **6**	76

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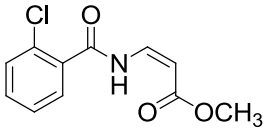
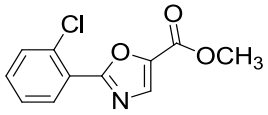
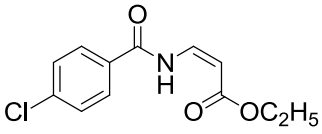
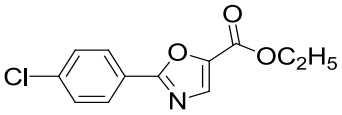
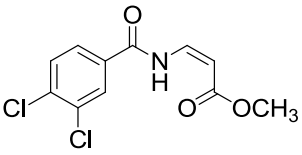
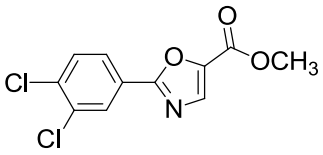
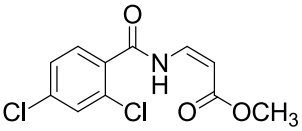
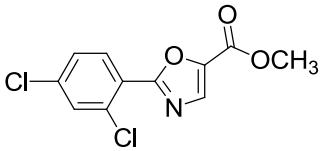
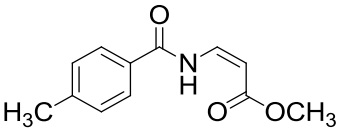
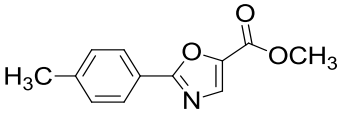
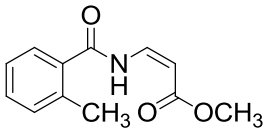
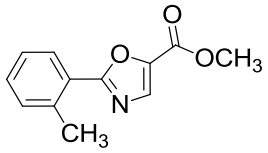
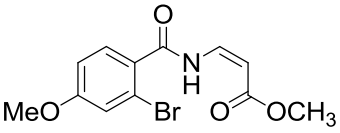
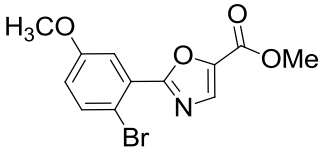
6		 **7**	83
7		 **8**	86
8		 **9**	93
9		 **10**	85
10		 **11**	91
11		 **12**	81
12		 **13**	74

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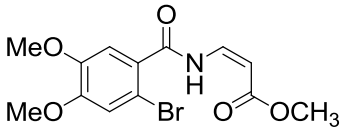
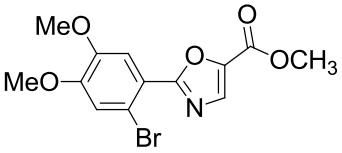
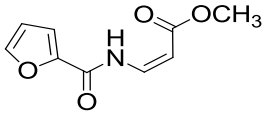
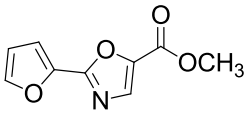
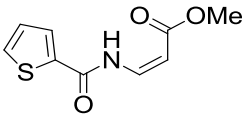
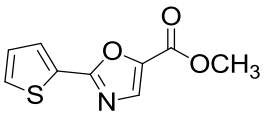
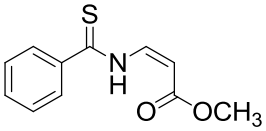
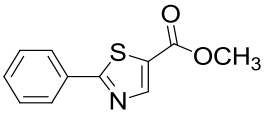
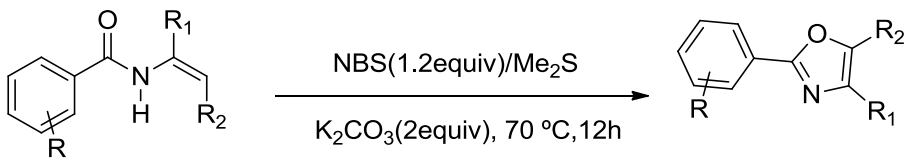
13		 **14**	81
14		 **15**	71
15		 **16**	75
16		 **17**	69

Reaction conditions: A mixture of enamide (100 mg), NBS (1.2 equiv), Me_2S (0.1 mL), in 4 mL of Toluene: DMF (3:1) was heated at 70 °C for overnight.

The substrate scope of the annulation reaction was further explored with the α- and β-substituted enamides to achieve 2,4,5-substituted oxazoles. Substituted enamides were prepared from the carbonylation of readily accessible enamines following the similar procedure reported elsewhere. As expected, under our optimized reaction conditions, 2,4,5-trisubstituted oxazoles (18-30) were obtained in good to excellent yield (Table 3).

Table 3. Synthesis of 2,4,5-substituted oxazoles



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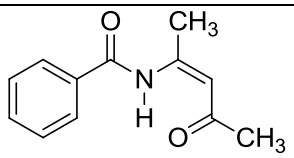
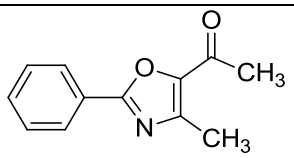
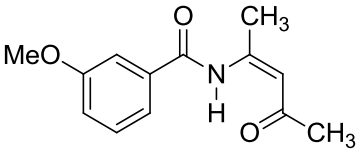
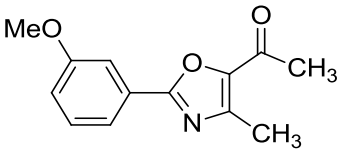
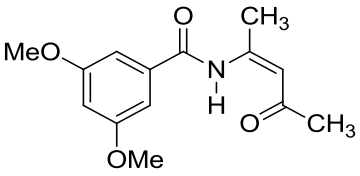
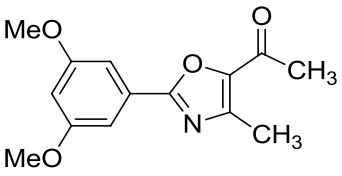
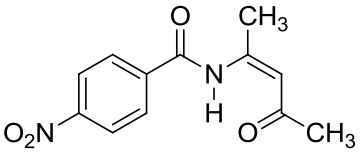
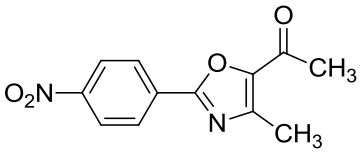
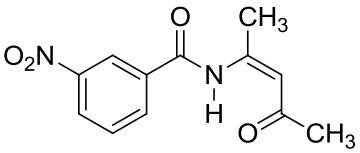
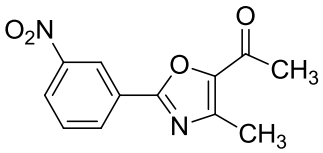
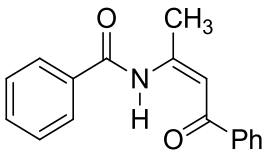
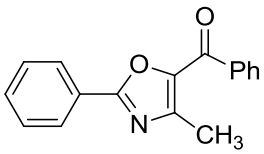
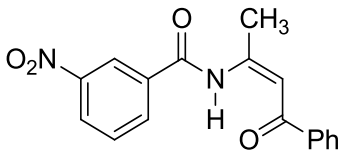
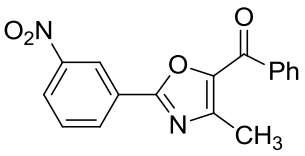
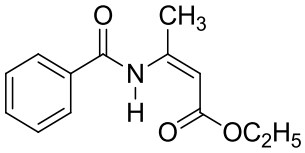
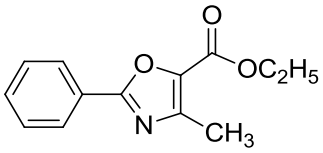
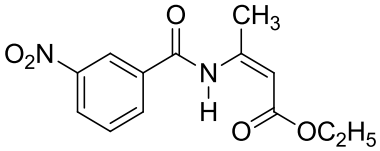
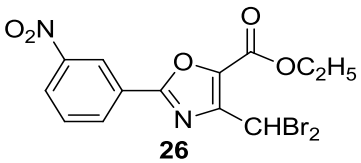
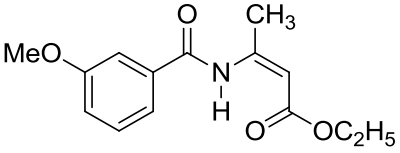
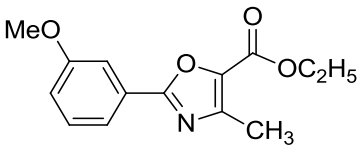
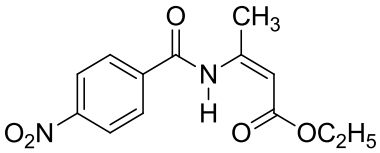
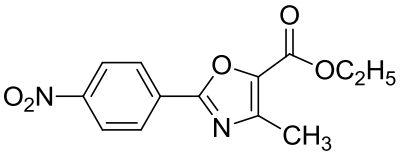
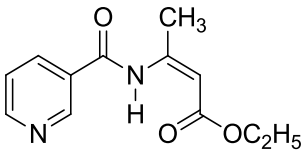
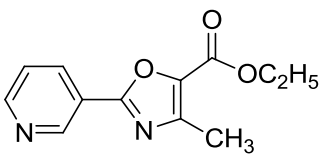
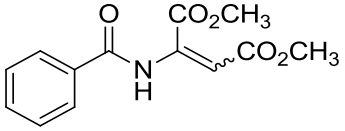
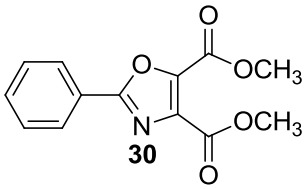
Entry	Enamide	Oxazole	Yield(%)
1		 **18**	88
2		 **19**	86
3		 **20**	90
4		 **21**	82
5		 **22**	92
6		 **23**	62

Continued….

7		 **24**	86
8		 **25**	88
9[a]		 **26**	47
10		 **27**	82
11		 **28**	87
12		 **29**	64
13		 **30**	67

Reaction conditions: A mixture of enamide (100 mg), NBS (1.2 equiv), Me_2S (0.1 mL), in 4 mL of toluene:DMF (3:1) was heated at 70 °C for overnight. [a] stirred at 70 °C for 24 h and only **26** was isolated.

Notably, different substituents on the aromatic ring did not affect the reaction to produce 2,4,5-trisubstituted oxazoles in moderate to good yield. Notably, electron- donating and -withdrawing groups α to the enamides prevent the reaction from occurring.

4.3 Conclusions

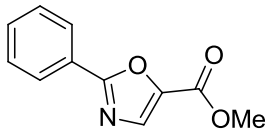
We have developed a transition metal-free protocol for the direct transformation of enamide into 2,5-substituted oxazoles in moderate to good yield. The reaction conditions are very mild and simple and do not require any inert atmosphere to result in good yield of the oxazoles. Mechanistic insight suggests that the reaction may proceed through the in situ formation of an oxazolium intermediate (e.g. **C**), which was subsequently oxidized to oxazoles. Furthermore, the present method is a suitable protocol to produce 2,4,5-trisubstituted oxazoles in good to excellent yield. The presence of an electron withdrawing β-substituent in the enamide is indispensable for the reaction to occur.

4.4 Experimental

General procedure for the synthesis of oxazoles

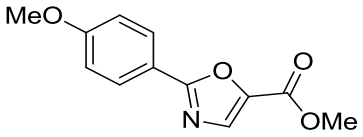
To a reaction mixture of enamide (100 mg), recrystallized NBS (1.2 equiv.) and K_2CO_3 (2 equiv.) in 4 mL of toluene: DMF (3:1), 0.1 mL of Me_2S was added. The reaction mixture was stirred at room temperature for 30 min and subsequently heated at 70 ºCfor overnight. Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate and water. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was subjected to column chromatography on silica gel [ethyl acetate/ petroleum ether (60–80 ºC)] to give the pure oxazoles.

Methyl 2-phenyloxazole-5-carboxylate (2)[21]



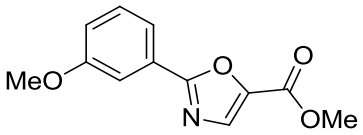
Yield: 78 mg (79%), white crystalline solid, mp 85–87 ºC. IR (KBr): 3114, 3030, 2952, 2849, 1712, 1630, 1579, 1535, 1473, 1447, 1348, 1308, 1246, 1205, 1142, 1093 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19–8.15 (m, 2H), 7.87 (s, 1H), 7.57–7.48 (m, 3H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 158.2, 142.0, 135.5, 131.6, 128.9, 127.2, 126.3, 52.2. MS (ESI, +ve) m/z (relative intensity) 204.06 ($[M + H]^+$, 100%).

Methyl 2-(4-methoxyphenyl)oxazole-5-carboxylate (3)



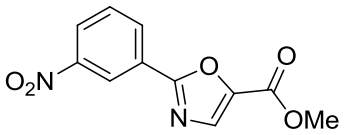
Yield: 75 mg (76%), white crystalline solid, mp 114–115 ºC. IR (KBr): 3154, 3098, 3002, 2949, 2834, 1731, 1611, 1586, 1489, 1436, 1358, 1307, 1254, 1193, 1150, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11–8.07 (m, 2H), 7.82 (s, 1H), 7.01–6.99 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.3, 158.3, 141.5, 135.6, 129.0, 118.9, 114.3, 55.4, 52.1. HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_4^+$ $[M + H]^+$ 234.0766, found 234.0765.

Methyl 2-(3-methoxyphenyl)oxazole-5-carboxylate (4)



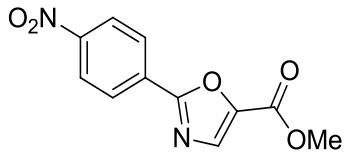
Yield: 79 mg (80%), white crystalline solid, mp 120–122 ºC. IR (KBr): 3439, 3002, 2951, 2845, 1735, 1579, 1534, 1470, 1435, 1355, 1307, 1263, 1219, 1194, 1151, 1090, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.78–7.74 (m, 1H), 7.68–7.65 (m, 1H), 7.42 (t, 1H, *J* = 8 Hz), 7.11–7.07 (m, 1H), 3.97 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 159.9, 158.2, 142.0, 135.5, 130.0, 127.4, 119.7, 118.4, 111.6, 55.5, 52.2. MS (ESI, +ve) m/z (relative intensity) 234.12 ($[M + H]^+$, 100%).

Methyl 2-(3-nitrophenyl)oxazole-5-carboxylate (5)



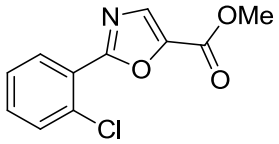
Yield: 80 mg (81%), white crystalline solid, mp 125–127 ºC. IR (KBr): 3115, 3061, 2986, 2915, 2862, 1725, 1635, 1589, 1528, 1396, 1345, 1302, 1252, 1156, 1013 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (m, 1H), 8.52–8.47 (m, 1H), 8.42–8.37 (m, 1H), 7.92 (s, 1H), 7.75 (t, 1H, *J* = 8 Hz), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 157.9, 148.6, 142.9, 135.5, 132.6, 130.2, 127.9, 123.1, 122.1, 52.5. MS (ESI, +ve) m/z (relative intensity) 248.14 ($[M + H]^+$, 100%).

Methyl 2-(4-nitrophenyl)oxazole-5-carboxylate (6)



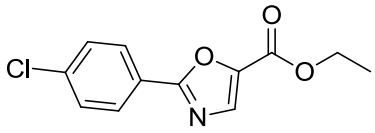
Yield: 75 mg (76%), white crystalline solid, mp 117–118 ºC. IR (KBr): 3065, 2975, 2858, 1719, 1639, 1586, 1528, 1386, 1342, 1312, 1263, 1165, 1068, 1013 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41–8.35 (m, 4H), 7.93 (s, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 157.8, 149.4, 143.1, 135.6, 131.6, 128.1, 124.2, 52.5. MS (ESI, +ve) m/z (relative intensity) 248.11 ($[M + H]^+$, 100%).

Methyl 2-(2-chlorophenyl)oxazole-5-carboxylate (7)



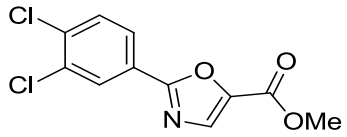
Yield: 82 mg (83%), white crystalline solid, mp 92–94 ºC. IR (KBr): 3064, 2921, 2851, 1728, 1586, 1527, 1450, 1356, 1303, 1151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.94 (s, 1H), 7.58–7.54 (m, 1H), 7.49– 7.38 (m, 2H), 3.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 158.1, 142.3, 135.1, 133.2, 132.1, 131.4, 131.4, 126.9, 125.2, 52.3. MS (ESI, +ve) m/z (relative intensity) 238.01 ($[M + H]^+$, 100%).

Ethyl 2-(4-chlorophenyl)oxazole-5-carboxylate (8)



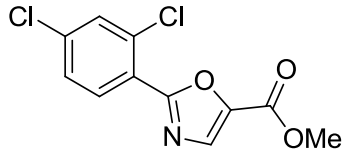
Yield: 85 mg (86%), white crystalline solid, mp 85–86 ºC. IR (KBr): 3062, 2925, 2856, 1716, 1629, 1583, 1535, 1461, 1349, 1312, 1156 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2 Hz), 7.85 (s, 1H), 7.49 (dd, 2H, J_1 = 6.8 Hz, J_2 = 2 Hz), 4.43 (q, 2H, J = 6.8 Hz), 1.42 (t, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 157.7, 142.4, 137.9, 135.3, 129.3, 128.5, 124.8, 61.5, 14.2. MS (ESI, +ve) m/z (relative intensity) 252.28 ($[M + H]^+$, 100%).

Methyl 2-(3,4-dichlorophenyl)oxazole-5-carboxylate (9)



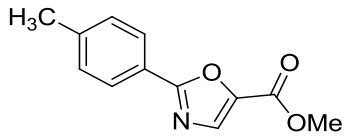
Yield: 92 mg (93%), white crystalline solid, mp 97–98 ºC. IR (KBr): 3086, 2952, 2921, 2845, 1733, 1627, 1580, 1524, 1452, 1396, 1304, 1198, 1139, 1031 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H, J = 2 Hz), 7.99 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2 Hz), 7.86 (s, 1H), 7.60 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 157.9, 142.5, 135.5, 133.6, 131.1, 128.9, 126.1, 126.0, 97.6, 52.4. HRMS (ESI) m/z calcd for $C_{11}H_8C_{l2}NO_3$ $[M + H]^+$ 271.9881, found 271.9876.

Methyl 2-(2,4-dichlorophenyl)oxazole-5-carboxylate (10)



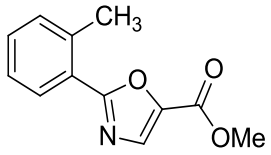
Yield: 84 mg (85%), white crystalline solid, mp 104-105 °C. IR (KBr): 3070, 2921, 2851, 1739, 1725, 1633, 1465, 1426, 1351, 1311, 1151.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 1H, J = 8.8 Hz), 7.93 (s, 1H), 7.58 (d, 1H, J = 1.2 Hz), 7.40 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2 Hz), 3.98 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 158.0, 142.4, 137.8, 135.1, 133.9, 132.1, 131.3, 127.5, 123.7, 52.4. HRMS (ESI) m/z calcd for $C_{11}H_8Cl_2NO_3^+[M + H]^+$ 271.9881, found 271.9876.

Methyl 2-p-tolyloxazole-5-carboxylate (11)



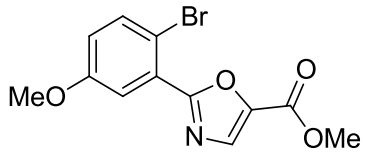
Yield: 90 mg (91%), white crystalline solid, mp 64-65 ºC. IR (KBr): 3109, 3002, 2957, 2918, 2851, 1714, 1613, 1570, 1542, 1486, 1437, 1352, 1310, 1246, 1182, 1148.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 2H, J = 8.4 Hz), 7.85 (s, 1H), 7.30 (m, 2H), 3.96 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.3, 142.2, 141.7, 135.6, 129.6, 127.2, 123.6, 52.2, 21.6. HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3^+[M + H]^+$ 218.0817, found 218.0832.

Methyl 2-o-tolyloxazole-5-carboxylate (12)



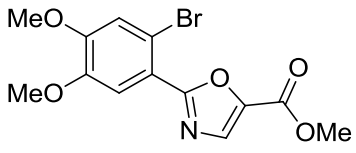
Yield: 80 mg (81%), white crystalline solid, mp 68-69 ºC. IR (KBr): 3120, 2954, 2918, 2840, 1734, 1716, 1627, 1586, 1525, 1485, 1451, 1353, 1304, 1190, 1147, 997.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13-8.08 (m, 1H), 7.89 (s, 1H), 7.44-7.37 (m, 1H), 7.35-7.29 (m, 2H), 3.96 (s, 3H), 2.73 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 158.3, 141.5, 138.4, 135.2, 131.8, 131.1, 129.5, 126.1, 125.3, 52.2, 22.0. HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3^+$[M+ H]$^+$218.0817, found 218.0807.

Methyl 2-(2-bromo-5-methoxyphenyl)oxazole-5-carboxylate (13)



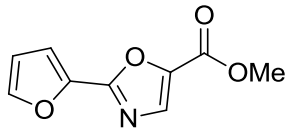
Yield: 73 mg (74 %), dark brown gummy liquid. IR (neat): 3109, 3008, 2951, 2840, 1735, 1571, 1524, 1460, 1436, 1344, 1309, 1231, 1194, 1150, 1039, 1017 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.62 (d, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 1.2 Hz), 6.93 (dd, 1H, J_1 = 9.2 Hz J_2 = 3.2 Hz), 3.97 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 158.7, 158.1, 142.3, 135.5, 134.9, 127.7, 119.0, 116.2, 111.9, 55.7, 52.3. HRMS (ESI) m/z calcd for $C_{12}H_{11}BrNO_4^+$[M + H]$^+$311.9871, found 311.9850.

Methyl 2-(2-bromo-4,5-dimethoxyphenyl)oxazole-5-carboxylate (14)



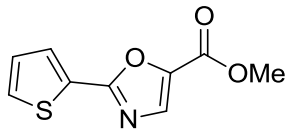
Yield: 80 mg (81 %), dark brown semi solid, IR (neat): 3308, 3070, 2951, 2918, 2845, 1712, 1629, 1586, 1493, 1459, 1432, 1248, 1205, 1078, 1041cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.53 (s, 1H), 7.17 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 158.2, 151.6, 148.3, 141.9, 135.0, 119.2, 117.1, 113.3, 112.9, 56.3, 56.2, 52.3.MS (ESI, +ve) m/z (relative intensity) 341.8 ([M + H]$^+$, 100%).

Methyl 2-(furan-2-yl)oxazole-5-carboxylate10 (15)



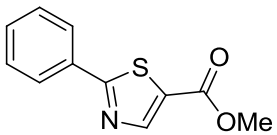
Yield: 70 mg (71 %), white crystalline solid, mp 1112-114 ºC.IR (KBr): 3386, 3127, 2921, 2850, 1736, 1628, 1581, 1517, 1436, 1350, 1308, 1256, 1195, 1195, 1151, 1096, 1014 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.63 (t, 1H, *J* = 1.2 Hz), 7.22 (t, 1H, *J* = 2 Hz), 6.58 (q, 1H, *J* = 1.8 Hz), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 156.5, 145.7, 141.9, 141.4, 135.4, 114.2, 112.2, 52.3. MS (ESI, +ve) m/z (relative intensity) 194.22 ($[M + H]^+$, 100%).

Methyl 2-(thiophen-2-yl)oxazole-5-carboxylate10 (16)



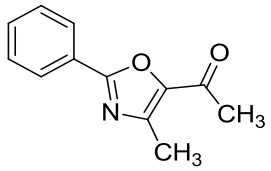
Yield: 74 mg (75 %), white crystalline solid, mp 108-110 ºC. IR (KBr): 3085, 3008, 2963, 2920, 2840, 1734, 1697, 1583, 1560, 1482, 1359, 1300, 1192, 1144cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, 1H, J_1 = 3.6 Hz, J2 = 1.2 Hz), 7.81 (s, 1H), 7.55 (dd, 1H, J_1 = 4 Hz, J_2 = 1.2 Hz), 7.17 (dd, 1H, J_1 = 5 Hz, J_2 = 4 Hz), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 158.1, 141.4, 135.6, 130.4, 129.9, 128.7, 128.3, 52.2. MS (ESI, +ve) m/z (relative intensity) 210.1 ($[M + H]^+$, 100%).

Methyl 2-phenylthiazole-5-carboxylate (17)



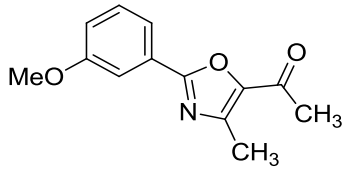
Yield: 68 mg (69 %) as yellow crystalline solid, mp 115-116 ºC. IR (KBr): 3058, 2991, 2944, 2924, 2834, 1707, 1625, 1517, 1454, 1312, 1252, 1194, 1150, 1093cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.03-7.98 (m, 2H), 7.53-7.48 (m, 3H), 3.95 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 161.8, 149.3, 132.8, 131.2, 129.1, 128.5, 126.9, 52.5. HRMS (ESI) m/z calcd for $C_{11}H_{10}NO_2S^+[M + H]^+$ 220.0432, found 220.0427.

1-(4-Methyl-2-phenyloxazol-5-yl)ethanone (18)[22]



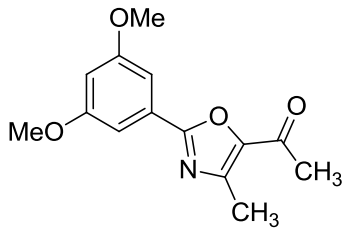
Yield: 87 mg (88%), white crystalline solid. mp 61-63 °C. IR (KBr): 3322, 3058, 3002, 2952, 2918, 2845, 1670, 1595, 1536, 1440, 1381, 1264, 1145, 1075.cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.10 (m, 2H), 7.55-7.47 (m, 3H), 2.58 (s, 3H), 2.57 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 161.4, 146.3, 145.1, 131.6, 128.9, 127.1, 126.3, 27.5, 13.8. MS (ESI, +ve) m/z (relative intensity) 202.14 ($[M + H]^+$, 100%).

1-(2-(3-Methoxyphenyl)-4-methyloxazol-5-yl)ethanone (19)



Yield: 85 mg (86%), yellow crystalline solid, mp 66-68 ºC. IR (KBr): 3064, 3002, 2923, 2837, 1677, 1582, 1527, 1469, 1433, 1387, 1358, 1322, 1277, 1236, 1182, 1141, 1080, 1042cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.69 (m, 1H), 7.65-7.62 (m, 1H), 7.42 (t, 1H, *J* = 8 Hz), 7.10-7.06 (m, 1H), 3.90 (s, 3H), 2.58 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 159.9, 146.2, 130.1, 119.6, 118.1, 111.7, 55.5, 27.5, 13.8. HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_3^+$[M + H]$^+$232.0974, found 232.0972.

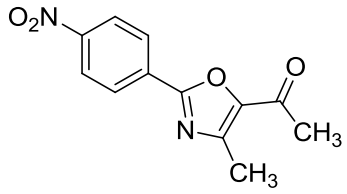
1-(2-(3,5-Dimethoxyphenyl)-4-methyloxazol-5-yl)ethanone (20)



Yield: 89 mg (90%), yellow crystalline solid, mp 69-71 ºC. IR (KBr): 3360, 3081, 3002, 2938, 2840, 1715, 1675, 1593, 1535, 1460, 1426, 1384, 1355, 1257, 1205, 1157, 1063 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.25 (s, 1H), 6.63 (t, 3H, *J* = 2.0 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 2.58 (s, 3H), 2.57 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 161.1,

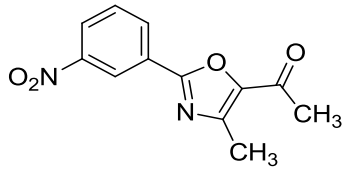
146.2, 127.9, 118.8, 104.9, 104.2, 97.3, 55.7, 55.6, 27.5, 13.8. HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_4^+$ $[M + H]^+$ 262.1079, found 262.1070.

1-(4-Methyl-2-(4-nitrophenyl)oxazol-5-yl)ethanone (21)



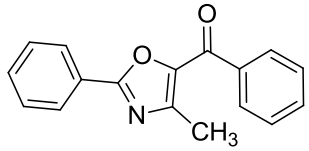
Yield: 81 mg (82 %), yellow crystalline solid, mp 83-84 ºC. IR (KBr): 3443,3054, 2923, 2836, 1676, 1581, 1537, 1470, 1433, 1387, 1358, 1322, 1276, 1235, 1182, 1140, 1080, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.39-8.35 (m, 2H), 8.32-8.28 (m, 2H), 2.61 (s, 3H), 2.60 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 187.4, 158.9, 149.3, 146.5, 145.8, 131.7, 127.9, 124.3, 27.6, 13.7. HRMS (ESI) m/z calcd for $C_{12}H_{11}N_2O_4^+$$[M + H]^+$ 247.0719, found 247.0713.

1-(4-Methyl-2-(3-nitrophenyl)oxazol-5-yl)ethanone (22)



Yield: 91 mg (92 %), yellow crystalline solid, mp 78-79 ºC. IR (KBr): 3075, 2919, 2840, 1677, 1573, 1520, 1384, 1347, 1307, 1260, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.95 (t, 1H, *J* = 1.2 Hz), 8.47 (s, 1H), 8.45 (s, 1H), 7.73 (t, 1H, *J* = 8 Hz), 2.62 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5, 158.8, 148.6, 146.3, 145.6, 132.6, 130.2, 128.0, 125.9, 121.9, 27.7, 13.7. HRMS (ESI) m/z calcd for $C_{12}H_{11}N_2O_4^+$ $[M + H]^+$ 247.0719, found 247.0713.

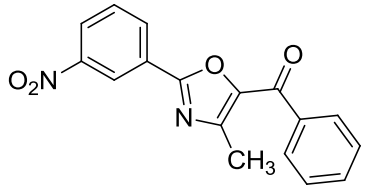
(4-Methyl-2-phenyloxazol-5-yl)(phenyl)methanone (23)



Yield: 61 mg (62 %), off-white crystalline solid, mp 62-64 ºC. IR (KBr): 3059, 2921, 2865, 1641, 1597, 1537, 1477, 1448, 1382, 1355, 1299, 1264, 1175, 1125 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.06 (m, 4H), 7.66-7.51 (m, 6H), 2.65 (s, 3H).^{13}C NMR (100 MHz,

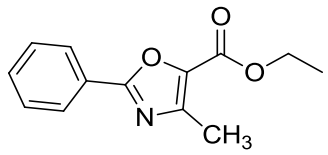
$CDCl_3$): δ 182.7, 161.8, 149.2, 144.8, 137.3, 132.8, 131.7, 129.3, 129.0, 128.5, 127.2, 14.3. MS (ESI, +ve) m/z (relative intensity) 264.11 ($[M + H]^+$, 100%).

(4-Methyl-2-(3-nitrophenyl)oxazol-5-yl)(phenyl)methanone (24)



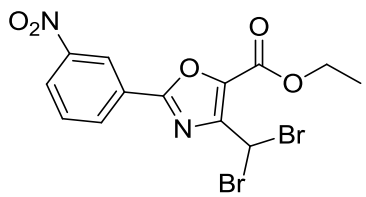
Yield: 85 mg (86 %), yellow crystalline solid, mp 78-79 ºC. IR (KBr): 3446, 3092, 2957, 2924, 2857, 1643, 1597, 1525, 1447, 1384, 1348, 1311, 1266, 1175, 1135, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.93 (t, 1H, *J* = 2 Hz), 8.45-8.36 (m, 2H), 8.07-8.03 (m, 2H), 7.76-7.55 (m, 4H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 159.2, 148.9, 148.7, 145.3, 137.0, 133.1, 132.5, 130.2, 129.2, 128.6, 128.0, 125.8, 122.1, 14.2.MS (ESI, +ve) m/z (relative intensity) 331.06 ($[M + Na]^+$, 100%).

Ethyl 4-methyl-2-phenyloxazole-5-carboxylate (25)[23]



Yield: 87 mg (88%), colorless oil. IR (neat): 3060, 2916, 2835, 1724, 1608, 1543, 1466, 1392, 1347, 1252, 1245, 1158, 1107, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.14-8.10 (m, 2H), 7.51-7.47 (m, 3H), 4.41 (q, 2H, *J* = 7.2 Hz), 2.54 (s, 3H), 1.42 (t, 3H, *J* = 7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 158.8, 147.06, 137.4, 131.4, 128.8, 127.1, 126.4, 61.0, 14.3, 13.5. MS (ESI, +ve) m/z (relative intensity) 232.12 ($[M + H]^+$, 100%).

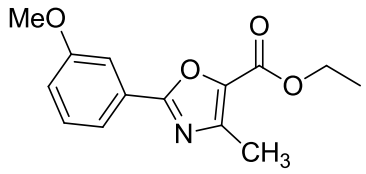
Ethyl 4-(dibromomethyl)-2-(3-nitrophenyl)oxazole-5-carboxylate (26)



Yield: 73 mg (47%); yellow crystalline solid, mp 128-130 ºC. IR (KBr): 3422, 3109, 2991, 2921, 2851, 1731, 1603, 1520, 1476, 1415, 1388, 1340, 1308, 1249, 1162, 1108, 1015cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 9.04 (t, 1H, *J* = 1.6 Hz), 8.59-8.55 (m, 1H), 8.46-8.41 (m, 1H),

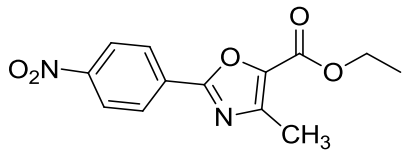
7.75 (t, 1H, *J* = 8 Hz), 7.32 (s, 1H), 4.52 (q, 2H, *J* = 7.2 Hz), 1.49 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (s), 157.0 (s), 148.7 (s), 147.5 (s), 133.3 (s), 133.1 (d), 130.2 (d), 127.3 (s), 126.5 (d), 122.4 (d), 62.5 (t), 27.5 (d), 14.2 (q). MS (ESI, +ve) m/z (relative intensity) 434.76 ($[M + H]^+$, 50%).

Ethyl 2-(3-methoxyphenyl)-4-methyloxazole-5-carboxylate (27)[24]



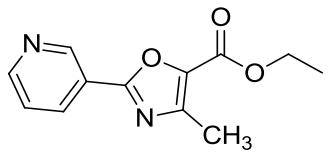
Yield: 81 mg (82%), white solid, mp 75-76 ºC. IR (KBr): 3065, 2929, 2829, 1711, 1605, 1540, 1469, 1397, 1348, 1272, 1235, 1152, 1108, 1039 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 1H, *J* = 8 Hz), 7.63 (d, 1H, J = 1.6 Hz), 7.38 (t, 1H, *J* = 8 Hz), 7.05 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2 Hz), 4.41 (q, 2H, *J* = 7.2 Hz), 3.88 (s, 3H), 2.54 (s, 3H), 1.42 (t, 3H, *J* =7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 159.8, 158.8, 147.0, 137.4, 129.9, 127.5, 119.7, 118.1, 111.5, 61.0, 55.5, 14.3, 13.5. MS (ESI, +ve) m/z (relative intensity) 262.14 ($[M + H]^+$, 100%).

Ethyl 4-methyl-2-(4-nitrophenyl)oxazole-5-carboxylate (28)



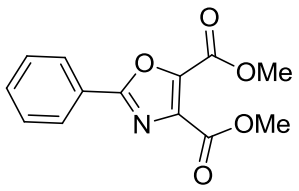
Yield: 86 mg (87%), yellow crystalline solid, mp 122-123 ºC IR (KBr): 3105, 3064, 2980, 2922, 2851, 1730, 1639, 1603, 1521, 1390, 1341, 1309, 1250, 1162, 1107, 1015cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36-8.29 (m, 4H), 4.45 (q, 2H, *J* = 7.2 Hz), 2.58 (s, 3H), 1.44 (t, 3H, *J* = 7.2 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.5, 149.2, 147.3, 138.6, 131.8, 128.0, 124.2, 61.4, 14.3, 13.4. HRMS (ESI) m/z calcd for $C_{13}H_{13}N_2O_5^+$ $[M + H]^+$ 277.0824, found 277.0819

Ethyl 4-methyl-2-(pyridin-3-yl)oxazole-5-carboxylate (29)[25]



Yield: 63 mg (64%) as yellow oil. IR (neat): 3075, 2929, 2784, 1772, 1708, 1640, 1426, 1371, 1297, 1246, 1189, 1006 cm $^{-1}$.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.79 (s, 1H), 8.40 (d, 1H, *J* = 8 Hz), 7.46 (s, 1H), 4.44 (q, 2H, *J* = 7.2 Hz), 2.57 (s, 3H), 1.44 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 158.6, 151.9, 148.3, 147.0, 138.0, 134.2, 123.7, 122.9, 61.3, 14.3, 13.4. MS (ESI, +ve) m/z (relative intensity) 233.05 ($[M + H]^+$, 100%).

2-Phenyl-oxazole-4,5-dicarboxylic acid dimethyl ester (30)[26]



Yield: 66 mg (67%), white solid, mp 78–79 ºC. IR (KBr): 3061, 2923, 2825, 1729, 1615, 1520, 1459, 1387, 1338, 1279, 1225, 1142, 1102, 1033 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21–8.16 (m, 2H), 7.58–7.48 (m, 3H), 4.02 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 161.0, 157.3, 141.9, 137.2, 132.2, 129.0, 127.5, 125.3, 53.0, 52.9. MS (ESI, +ve) m/z (relative intensity) 262.12 ($[M + H]^+$, 100%).

4.5 References

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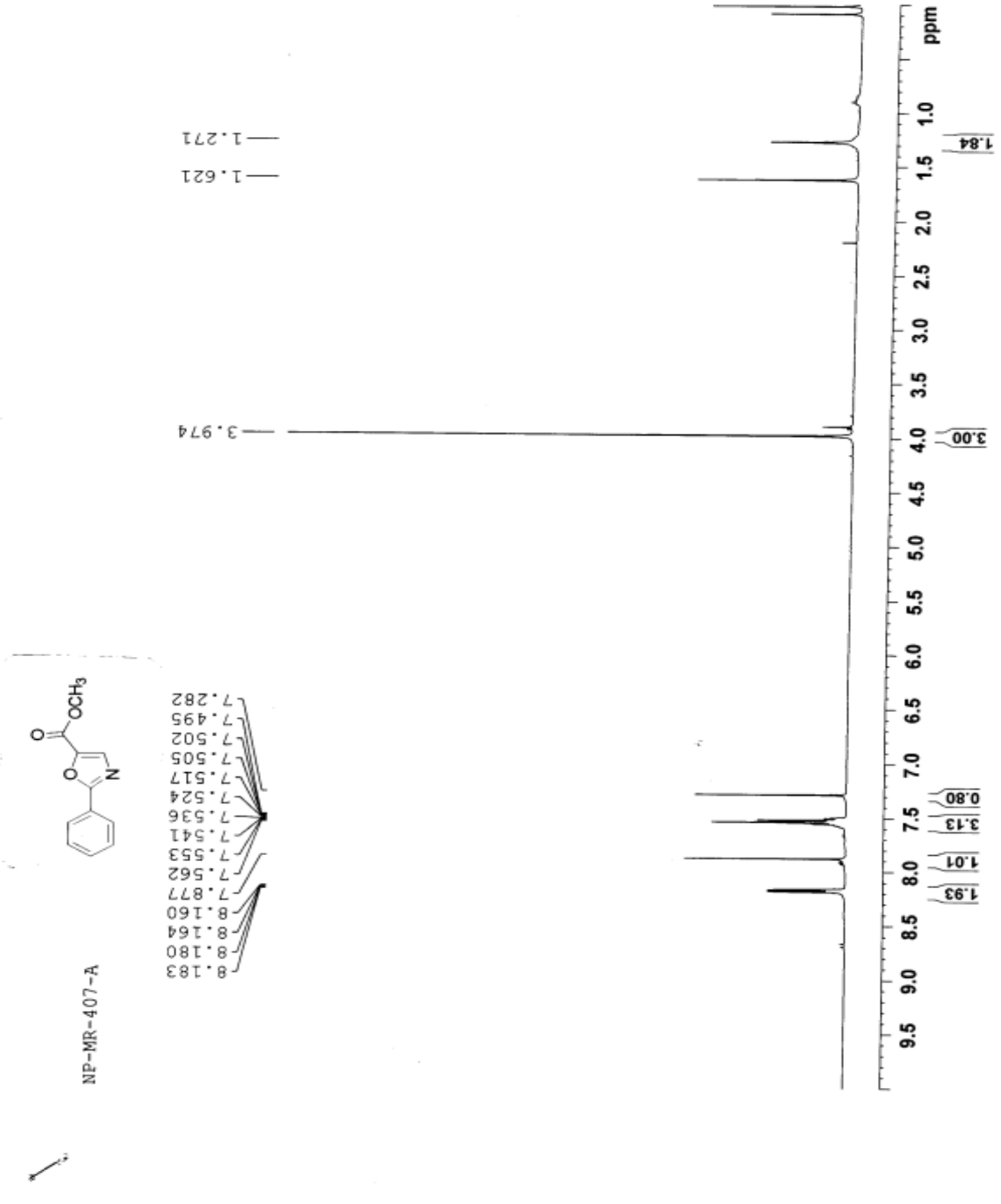
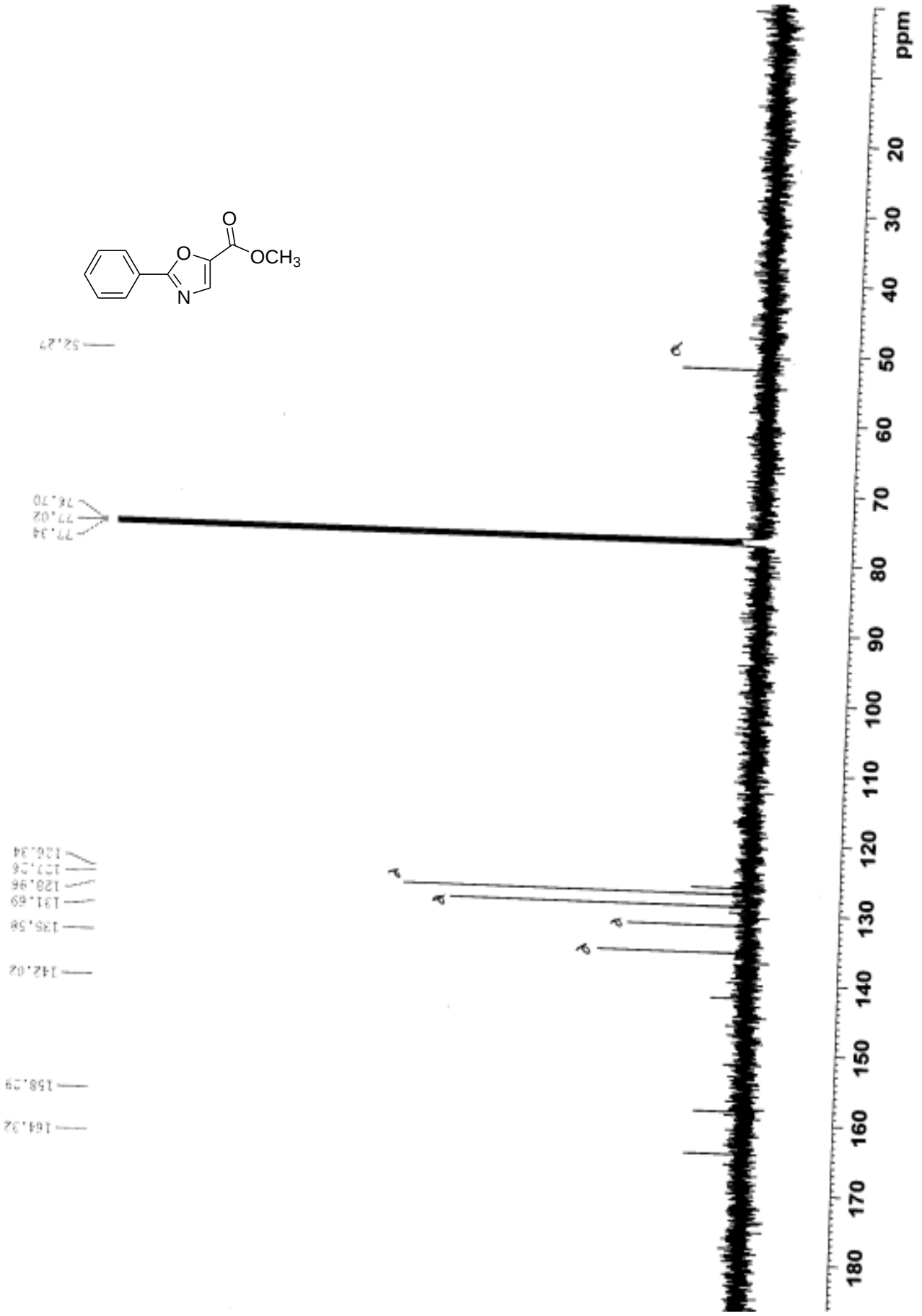
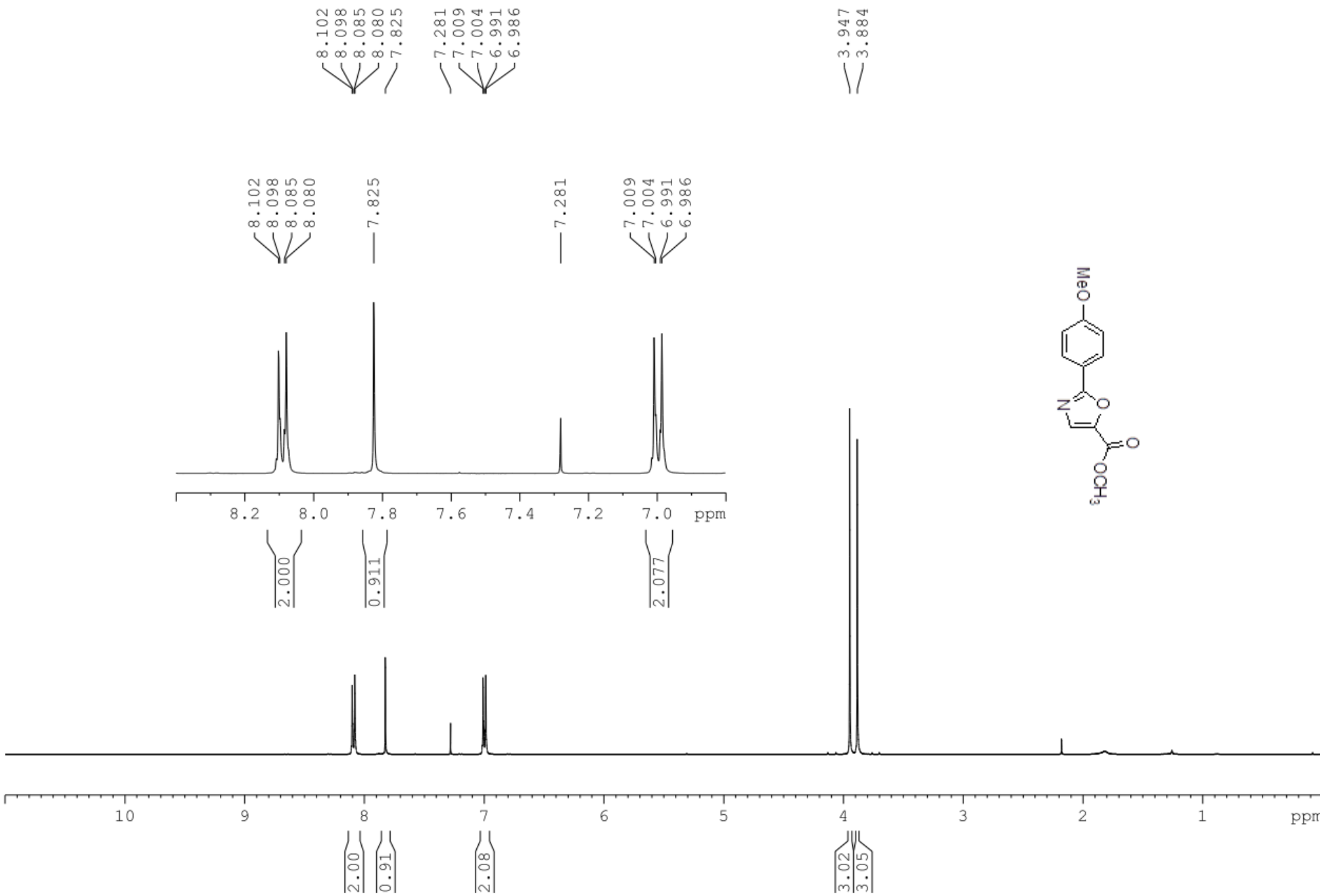
4.6 Selected NMR Spectra

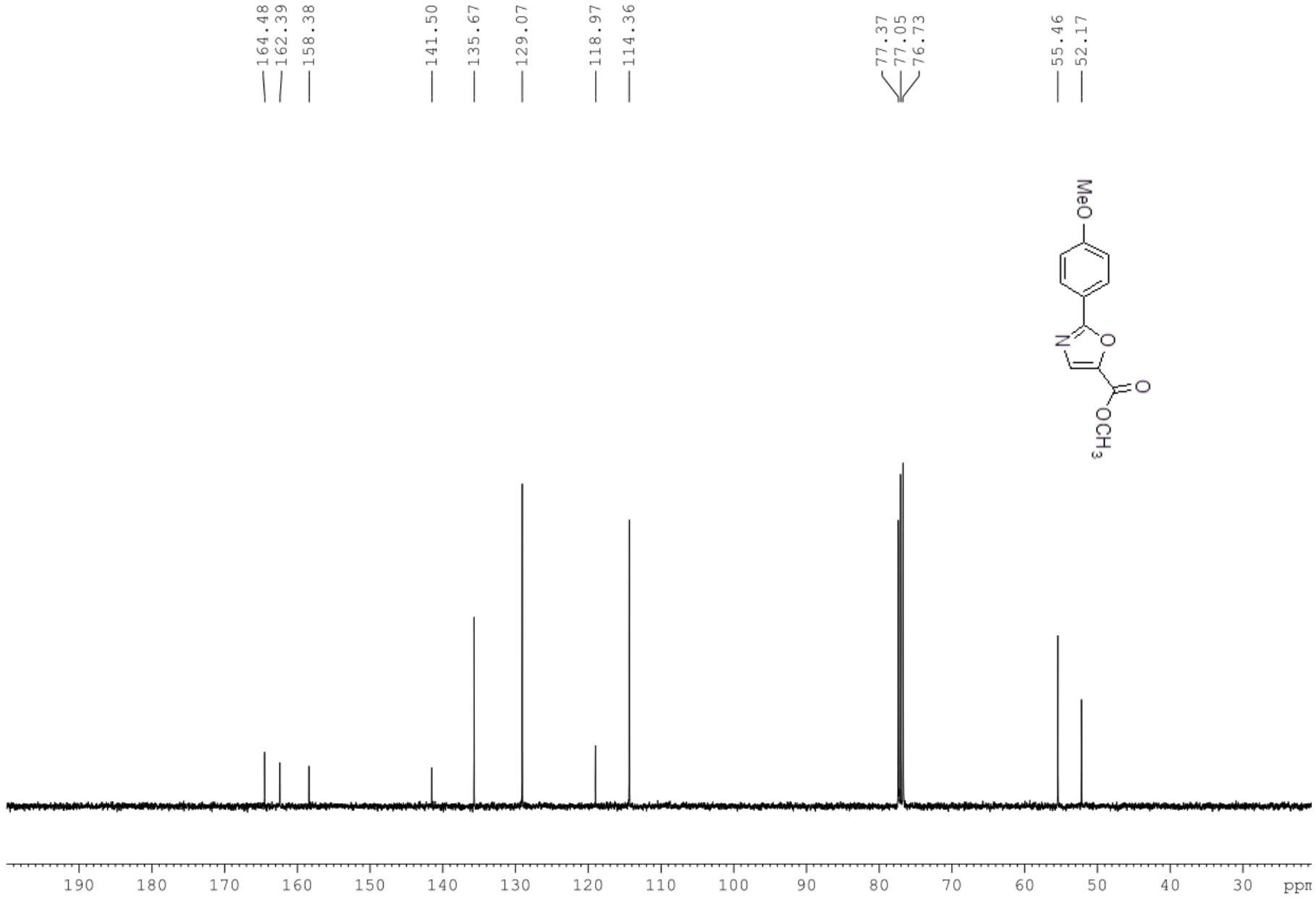



O
O
OCH3
N
52.27
76.70
77.02
77.34
130.34
131.26
128.96
131.69
135.58
142.02
158.29
164.32
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

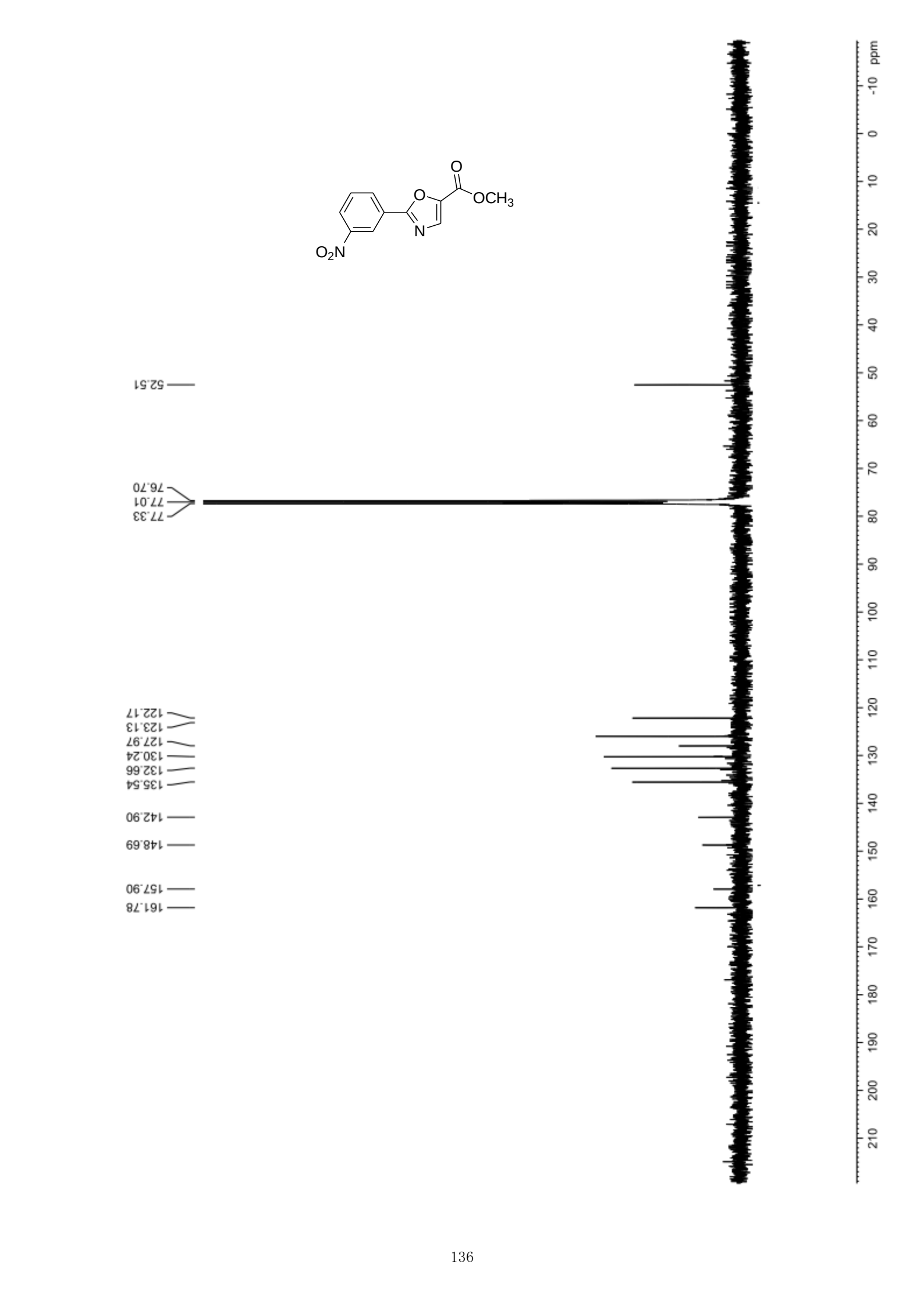
NP-DN-X 1H

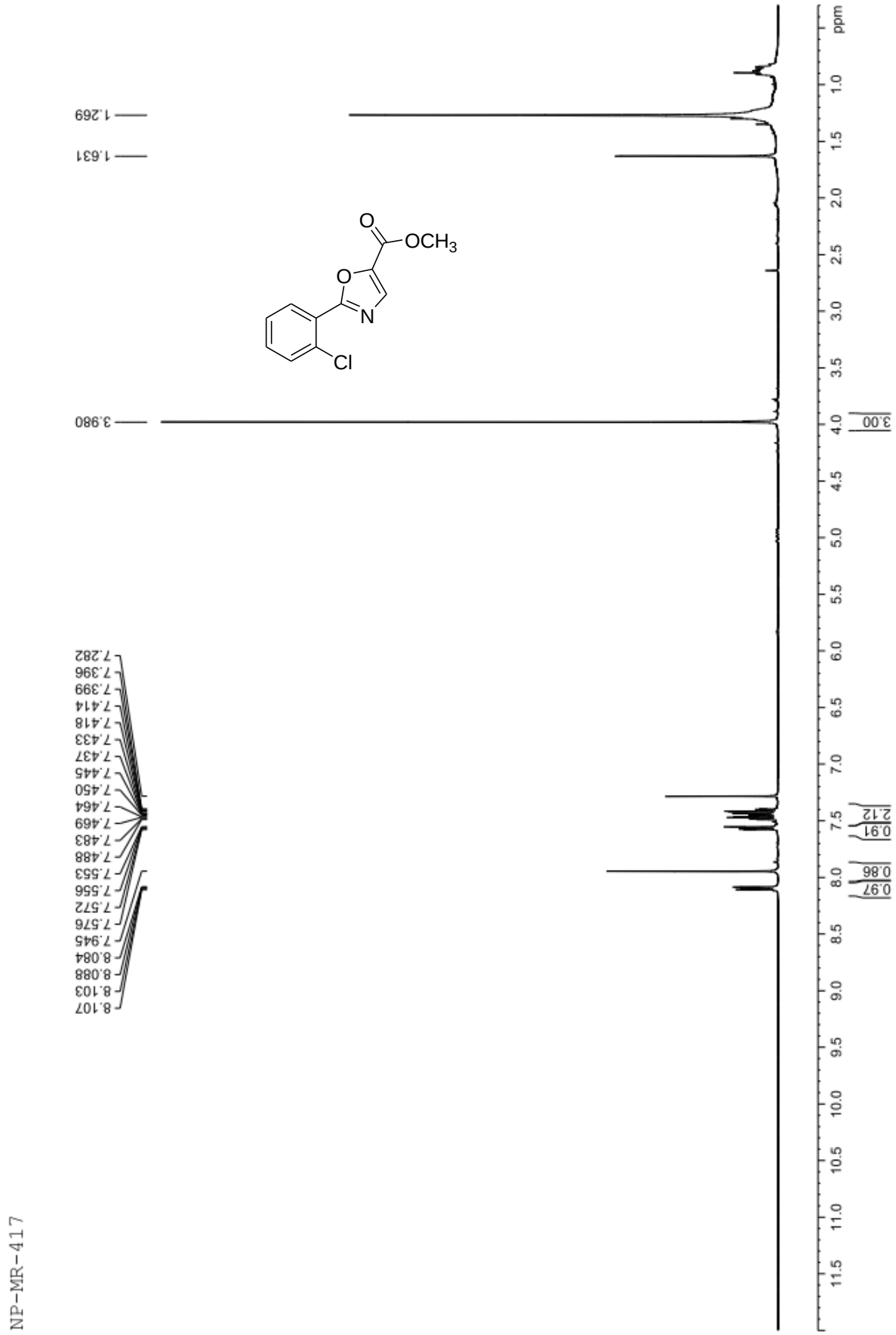

8.102
8.098
8.085
8.080
7.825
7.281
7.009
7.004
6.991
6.986
3.947
3.884
MeO
N
O
O
OCH3
8.2
8.0
7.8
7.6
7.4
7.2
7.0
ppm
2.000
0.911
2.077
10
9
8
7
6
5
4
3
2
1
ppm
2.00
0.91
2.08
3.02
3.05

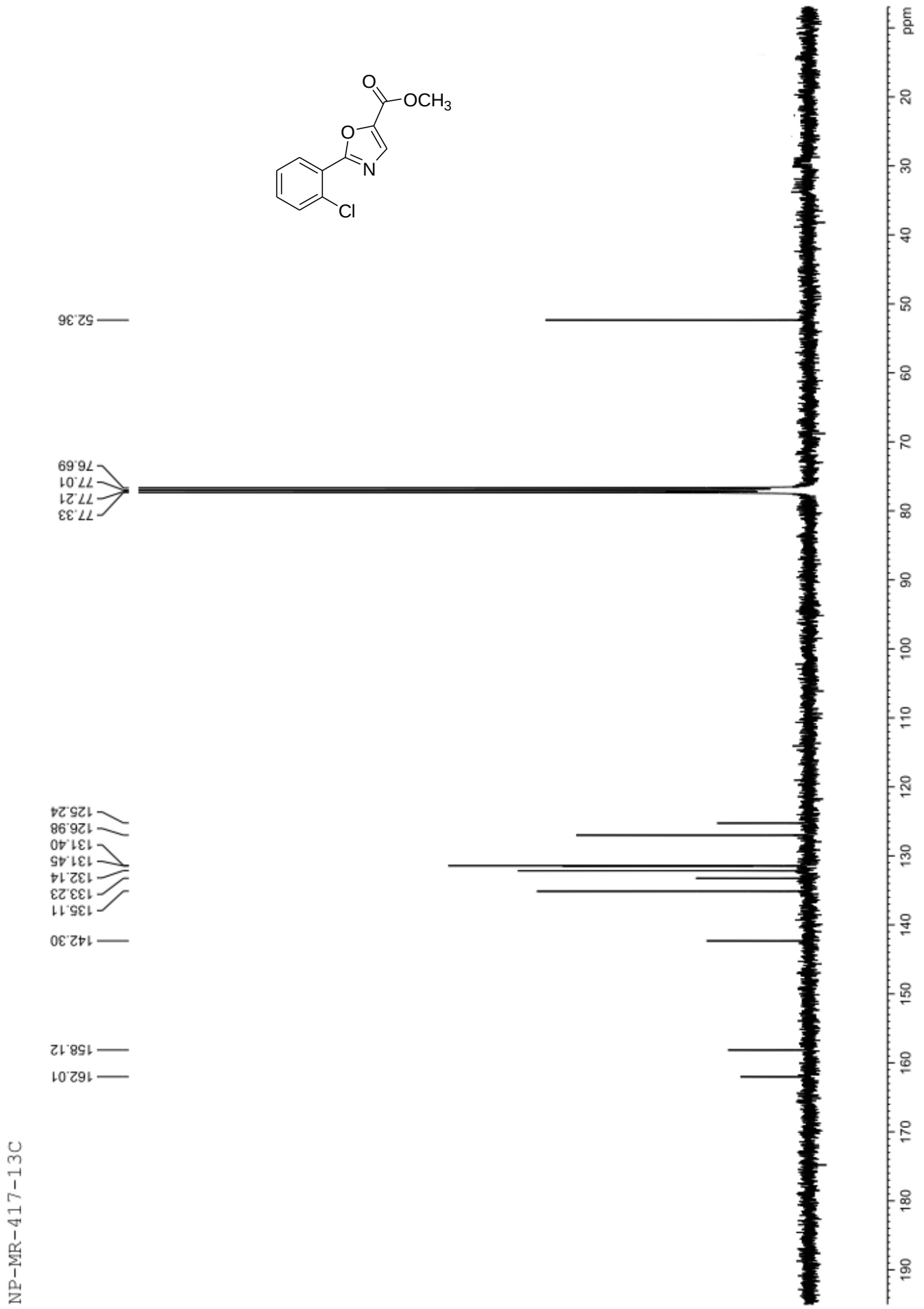
NP-DN-X 13C

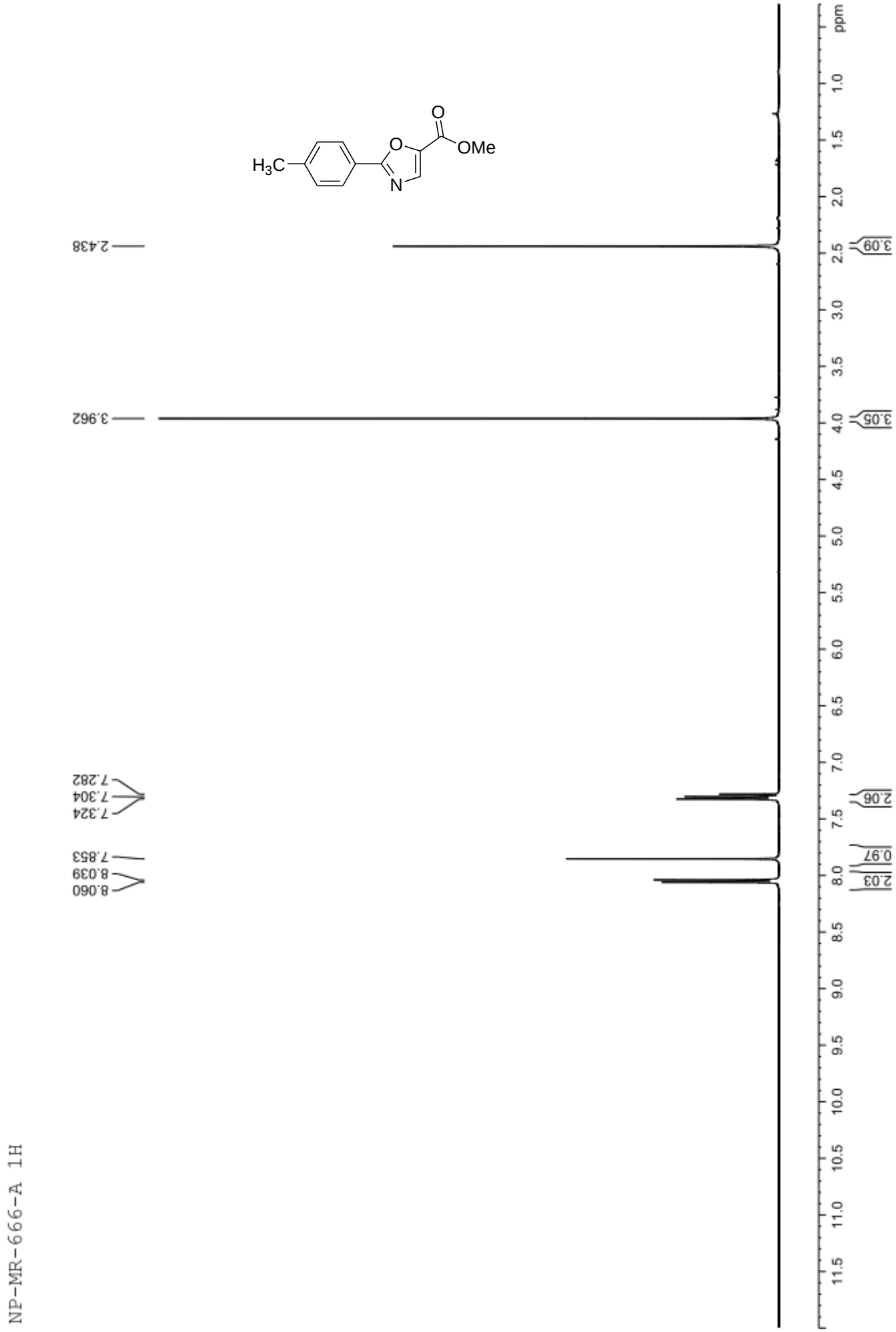

164.48
162.39
158.38
141.50
135.67
129.07
118.97
114.36
77.37
77.05
76.73
55.46
52.17
MeO
N
O
O
O
OCH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

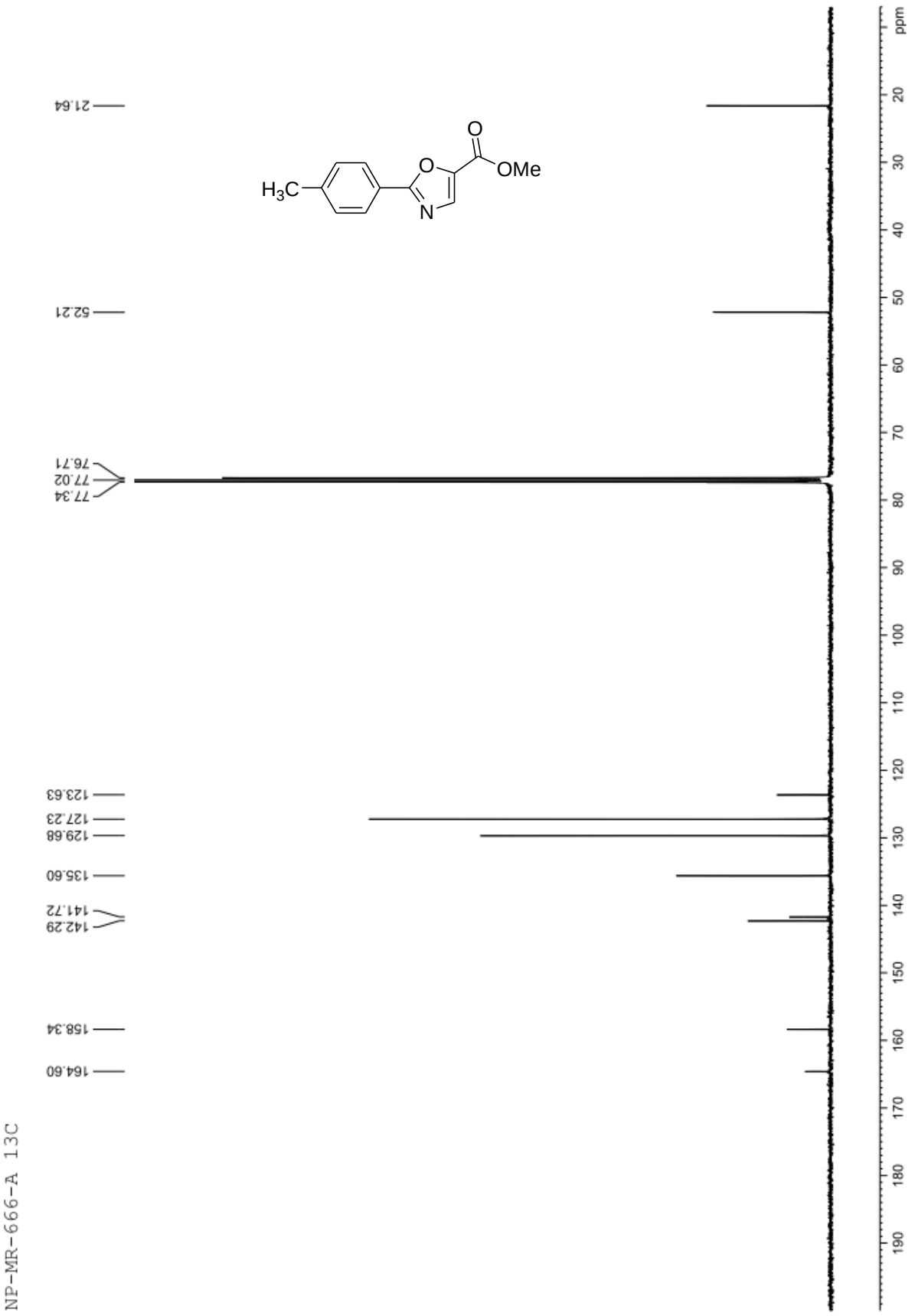
1.630
4.002
7.282
7.738
7.758
7.922
8.388
8.390
8.394
8.396
8.409
8.411
8.414
8.416
8.484
8.488
8.491
8.504
8.507
8.510
9.009
9.014
9.019
3.34
1.18
1.00
1.16
1.19
0.97
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
O
O
OCH3
N
O2N

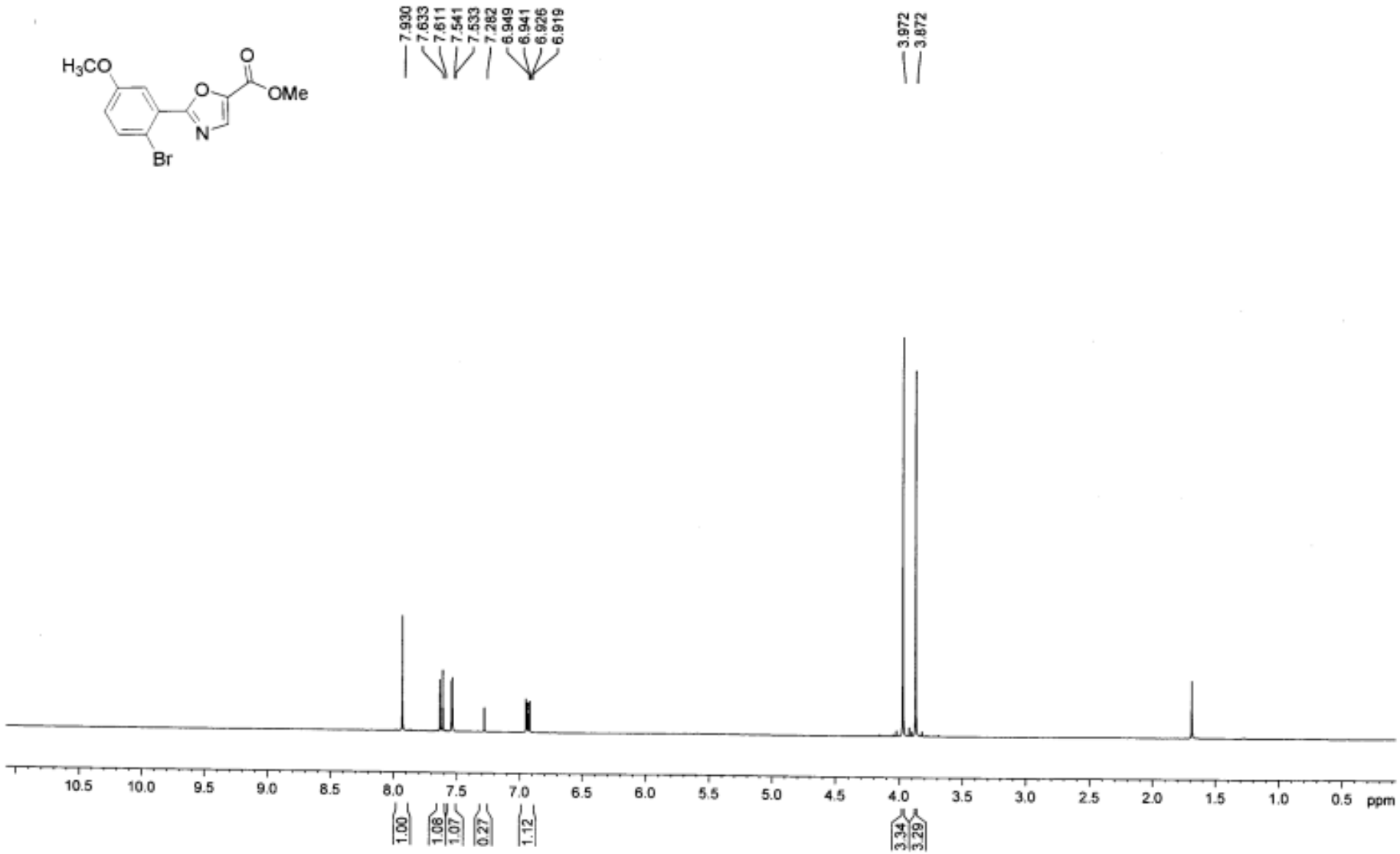

O
O
OCH3
N
O2N
52.51
76.70
77.01
77.33
122.17
123.13
127.97
130.24
132.66
135.54
142.90
148.69
157.90
161.78
ppm


NP-MR-417
1.269
1.631
3.980
7.282
7.396
7.399
7.414
7.418
7.433
7.437
7.445
7.450
7.464
7.469
7.483
7.488
7.553
7.556
7.572
7.576
7.945
8.084
8.088
8.103
8.107
O
OCH3
O
N
Cl
ppm
3.00
2.12
0.91
0.86
0.97


NP-MR-417-13C
O
OCH3
O
N
Cl
52.36
76.69
77.01
77.21
77.33
125.24
126.98
131.40
131.45
132.14
133.23
135.11
142.30
158.12
162.01
ppm


NP-MR-666-A 1H
O
OMe
H_3C
O
N
2.438
3.962
7.282
7.304
7.324
7.853
8.039
8.060
3.09
3.05
2.06
0.97
2.03
ppm


NP-MR-666-A 13C
21.64
52.21
76.71
77.02
77.34
123.63
127.23
129.68
135.60
141.72
142.29
158.34
164.60
O
O
OMe
H_3C
N
ppm


H3CO
O
OMe
N
Br
7.930
7.633
7.611
7.541
7.533
7.282
6.949
6.941
6.926
6.919
3.872
3.872
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
0.5
ppm
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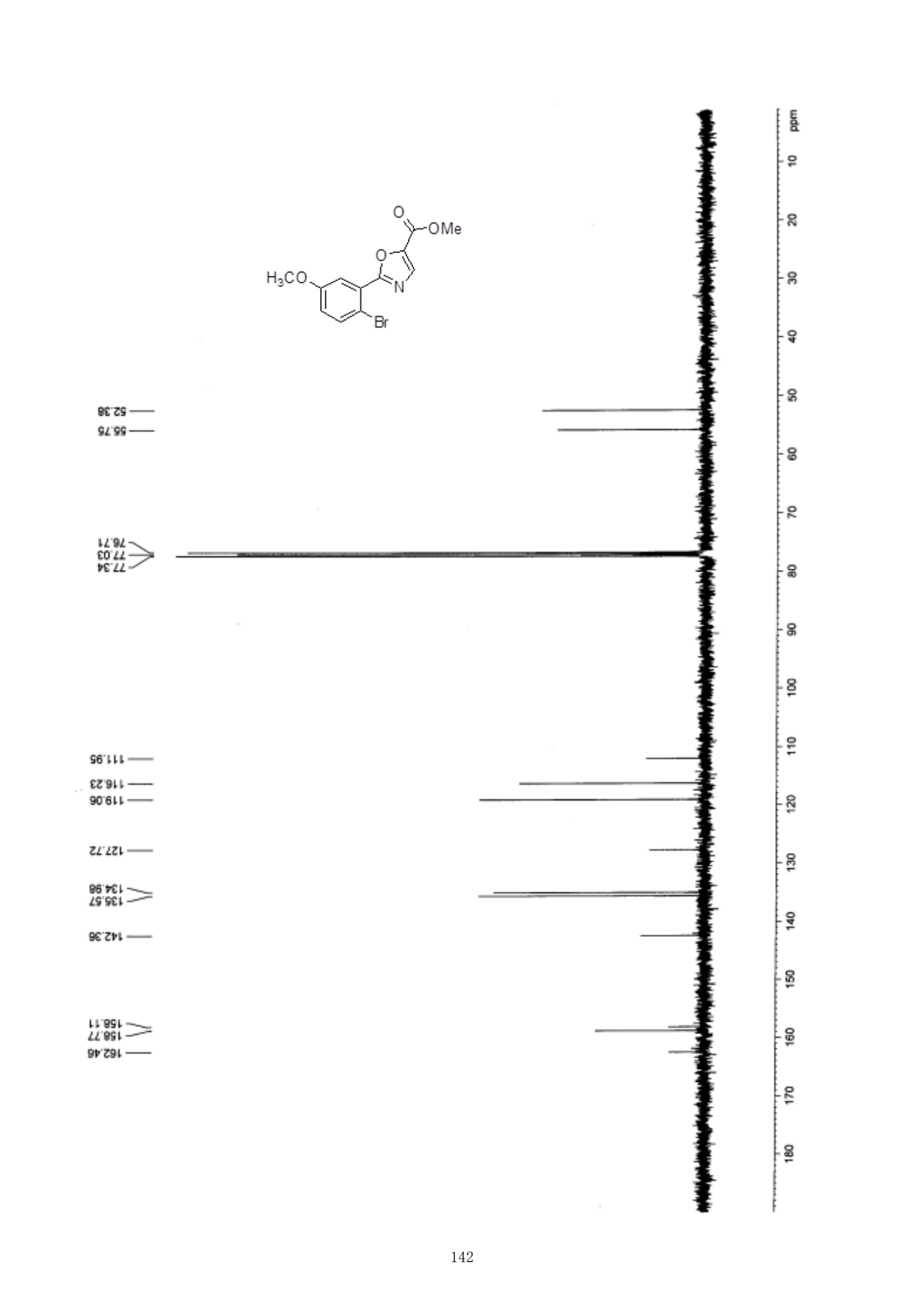
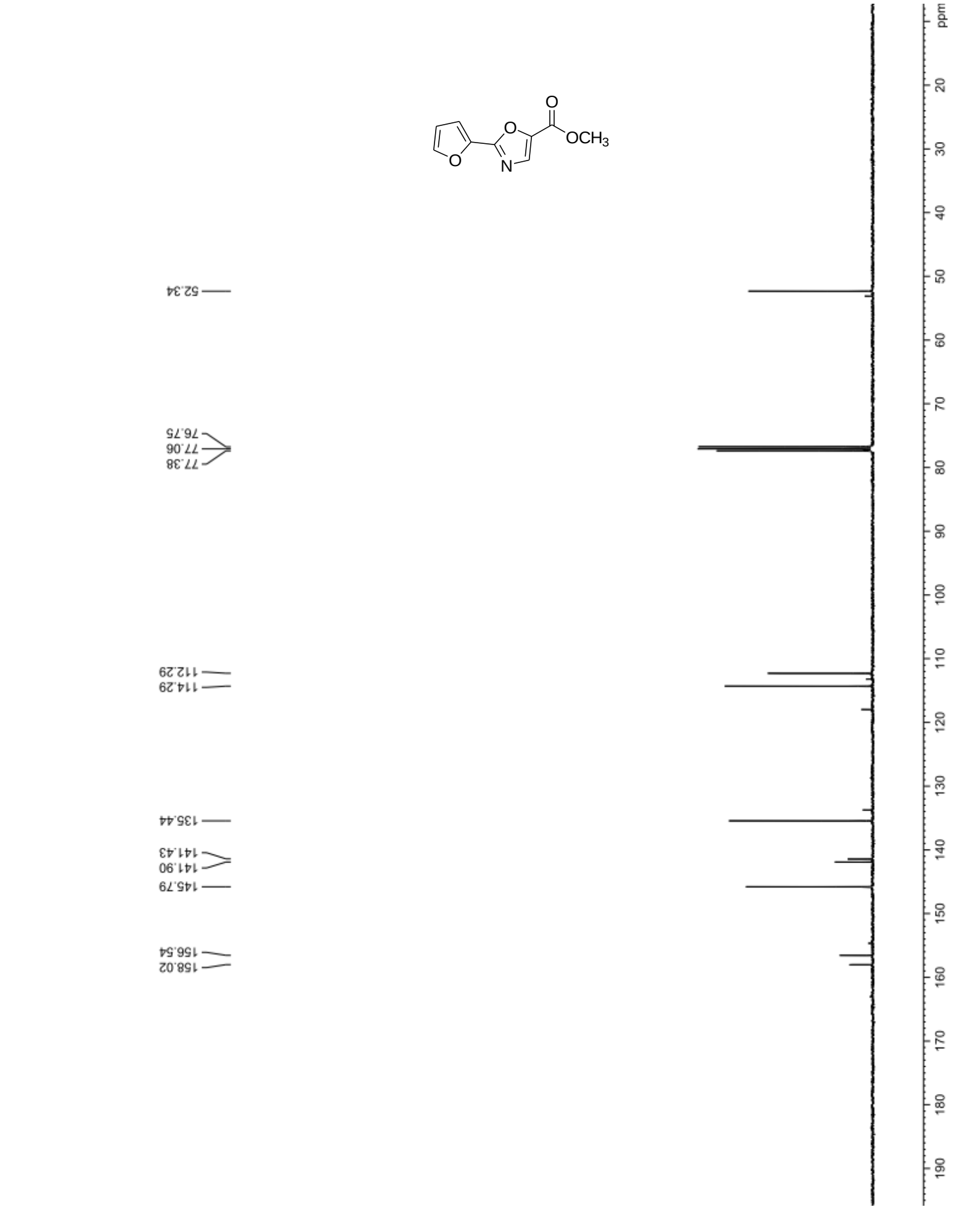
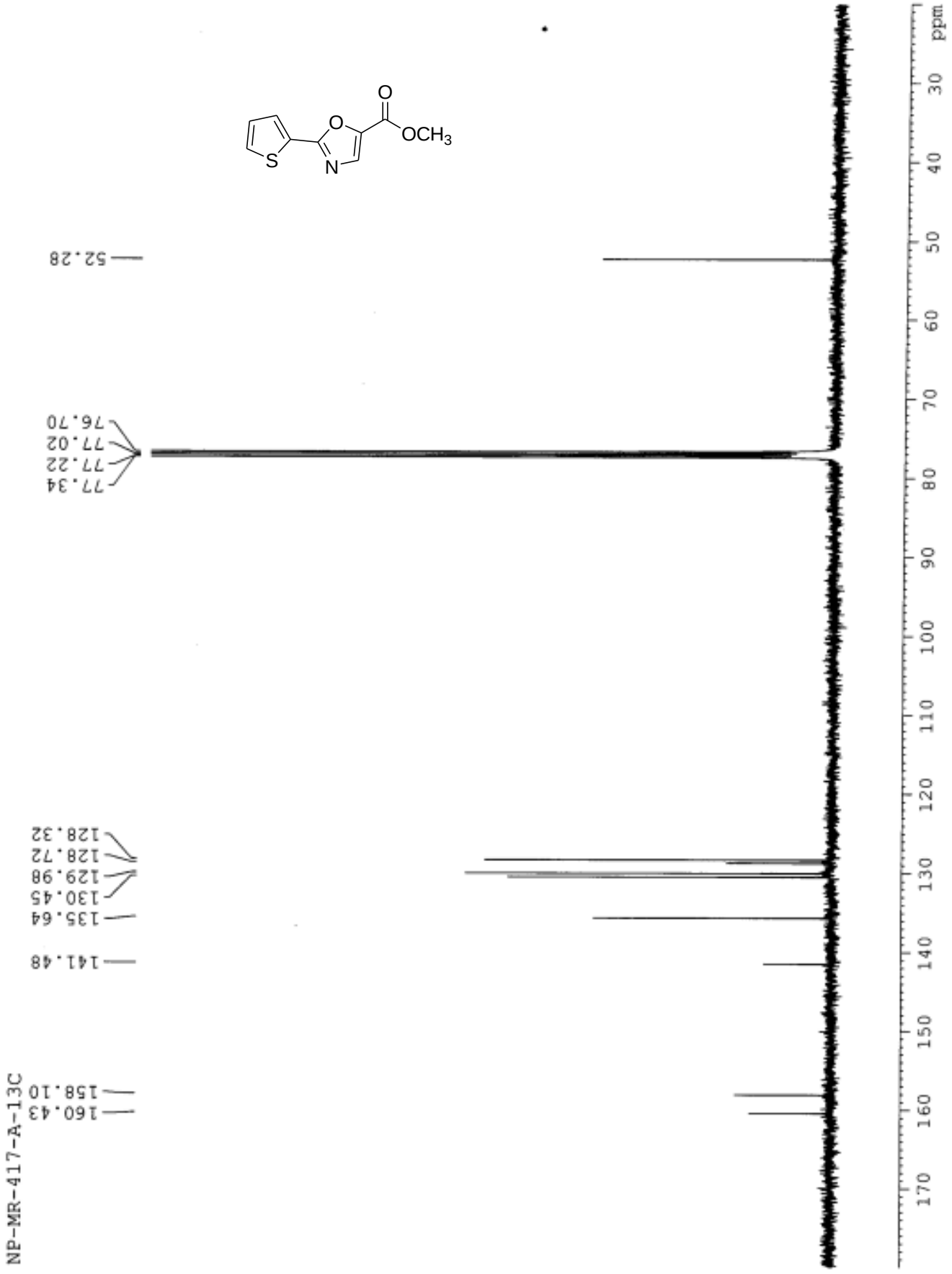
1.08
1.07
0.27
1.12
3.34
3.29


O
OMe
O
H3CO
N
Br
52.38
55.75
76.71
77.03
77.34
111.95
116.23
119.06
127.72
134.98
135.57
142.36
158.11
158.77
162.46
ppm

O
O
OCH3
O
N
3.941
6.580
6.584
6.588
6.593
7.219
7.228
7.229
7.627
7.630
7.632
7.833
3.15
1.06
1.03
1.00
1.00
ppm


O
O
N
O
OCH3
52.34
76.75
77.06
77.38
112.29
114.29
135.44
141.43
141.90
145.79
156.54
158.02
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

NP-MR-417-A
7.873
7.870
7.864
7.861
7.819
7.567
7.564
7.554
7.551
7.282
7.190
7.180
7.177
7.168
3.962
1.635
3.06
1.01
0.90
0.95
1.01
ppm
1
2
3
4
5
6
7
8
9
O
OCH3
O
N
S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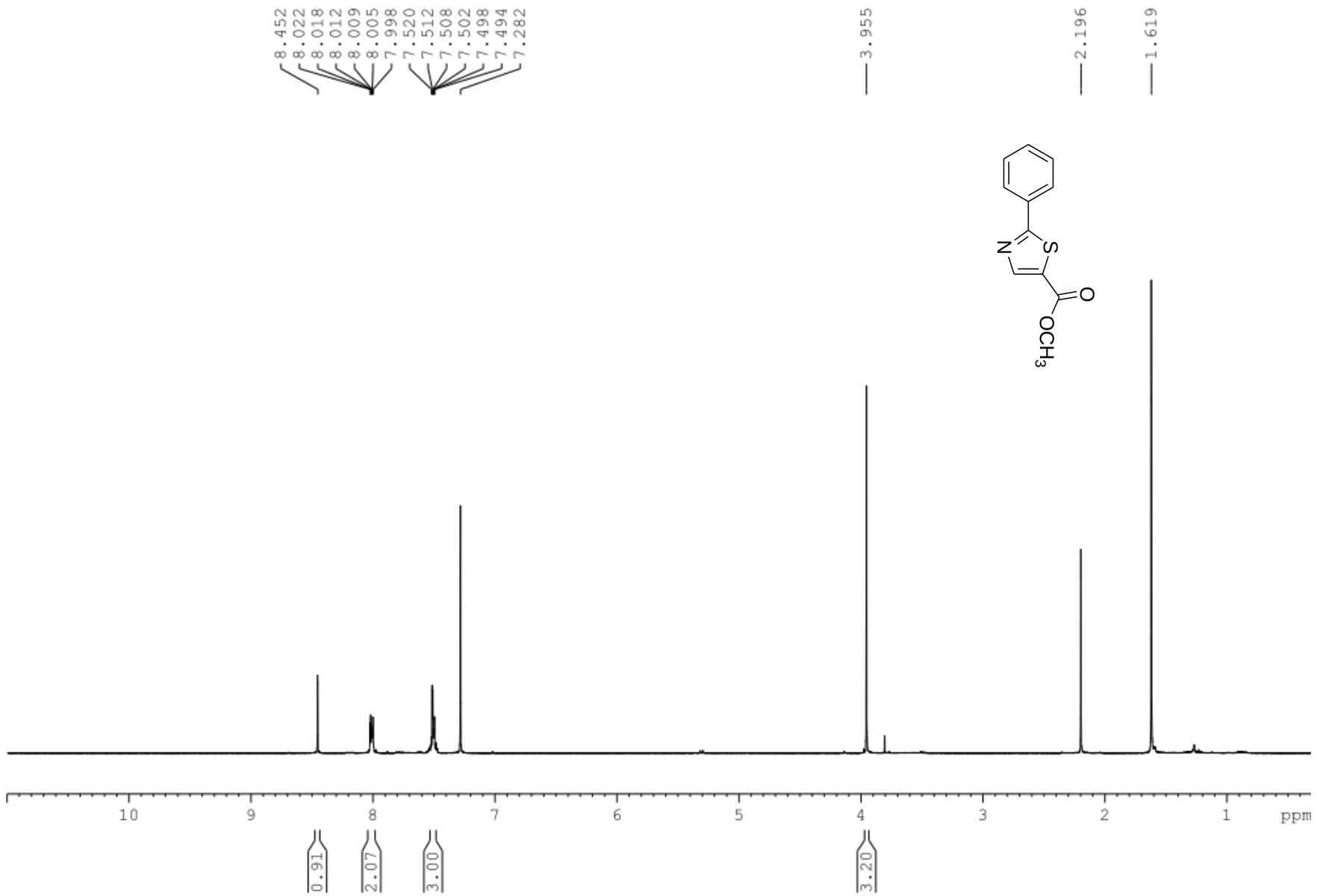
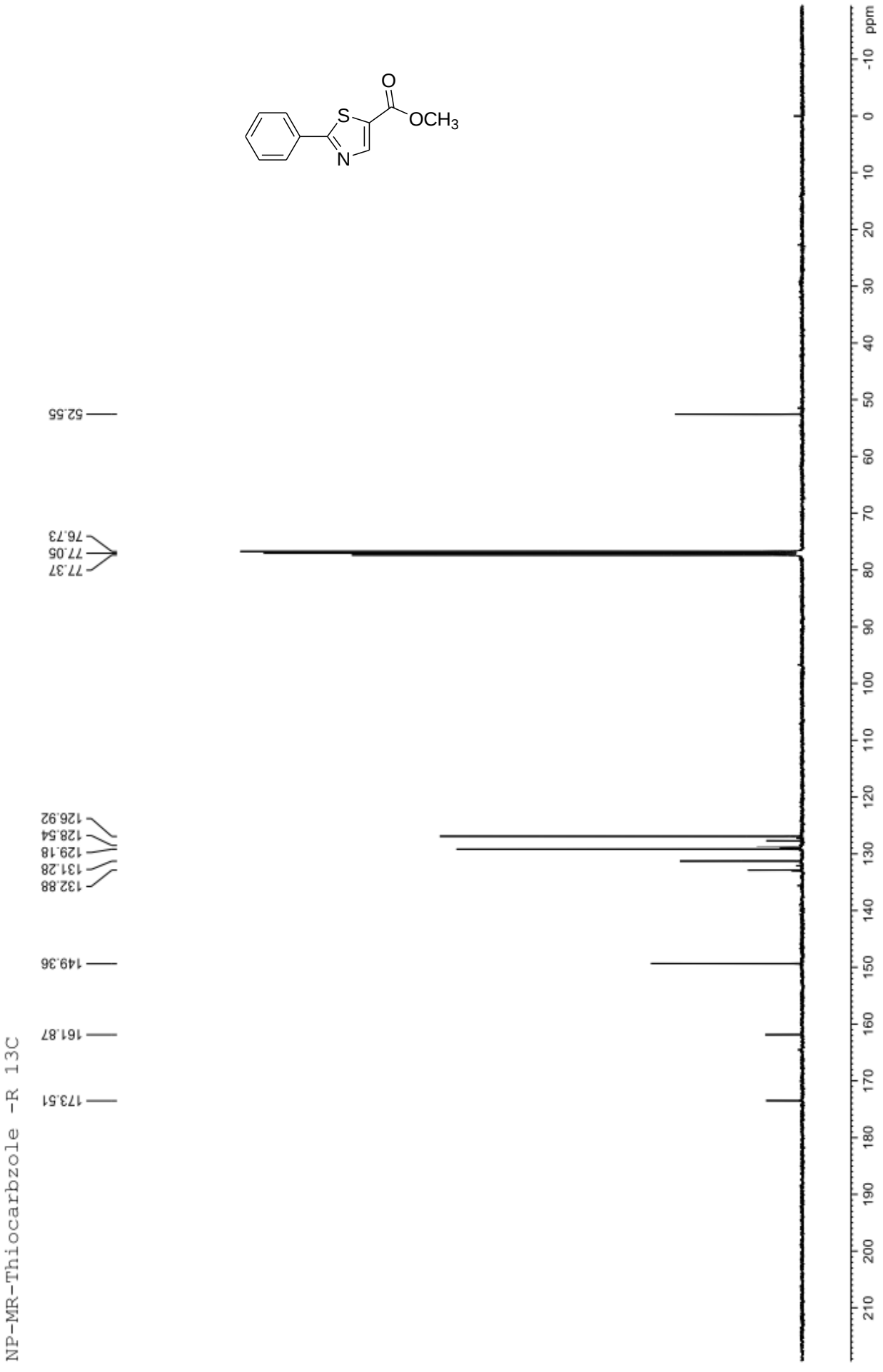
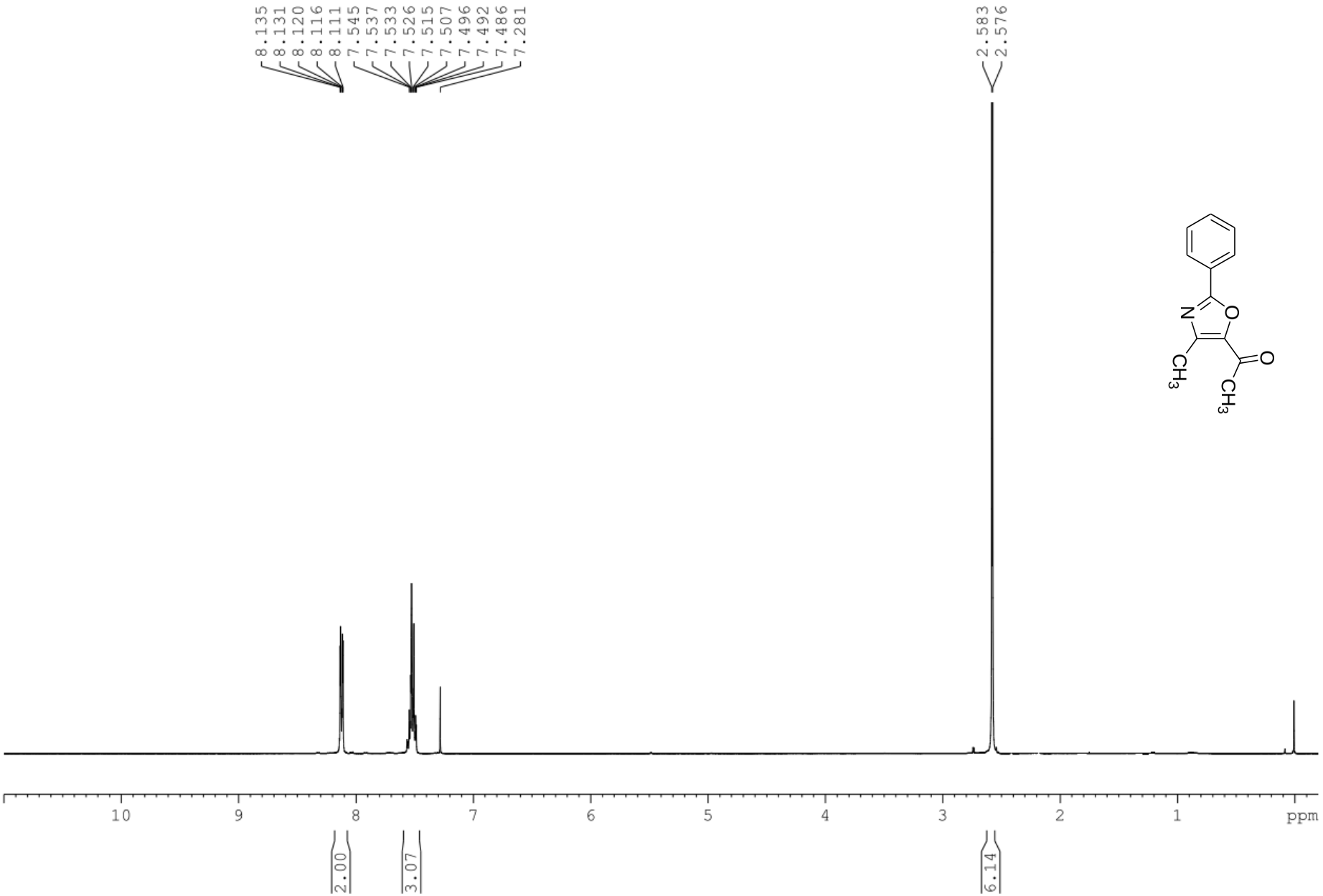
158.10
141.48
135.64
130.45
129.98
128.72
128.32
77.34
77.22
77.02
76.70
52.28
O
O
N
S
OCH3
ppm
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

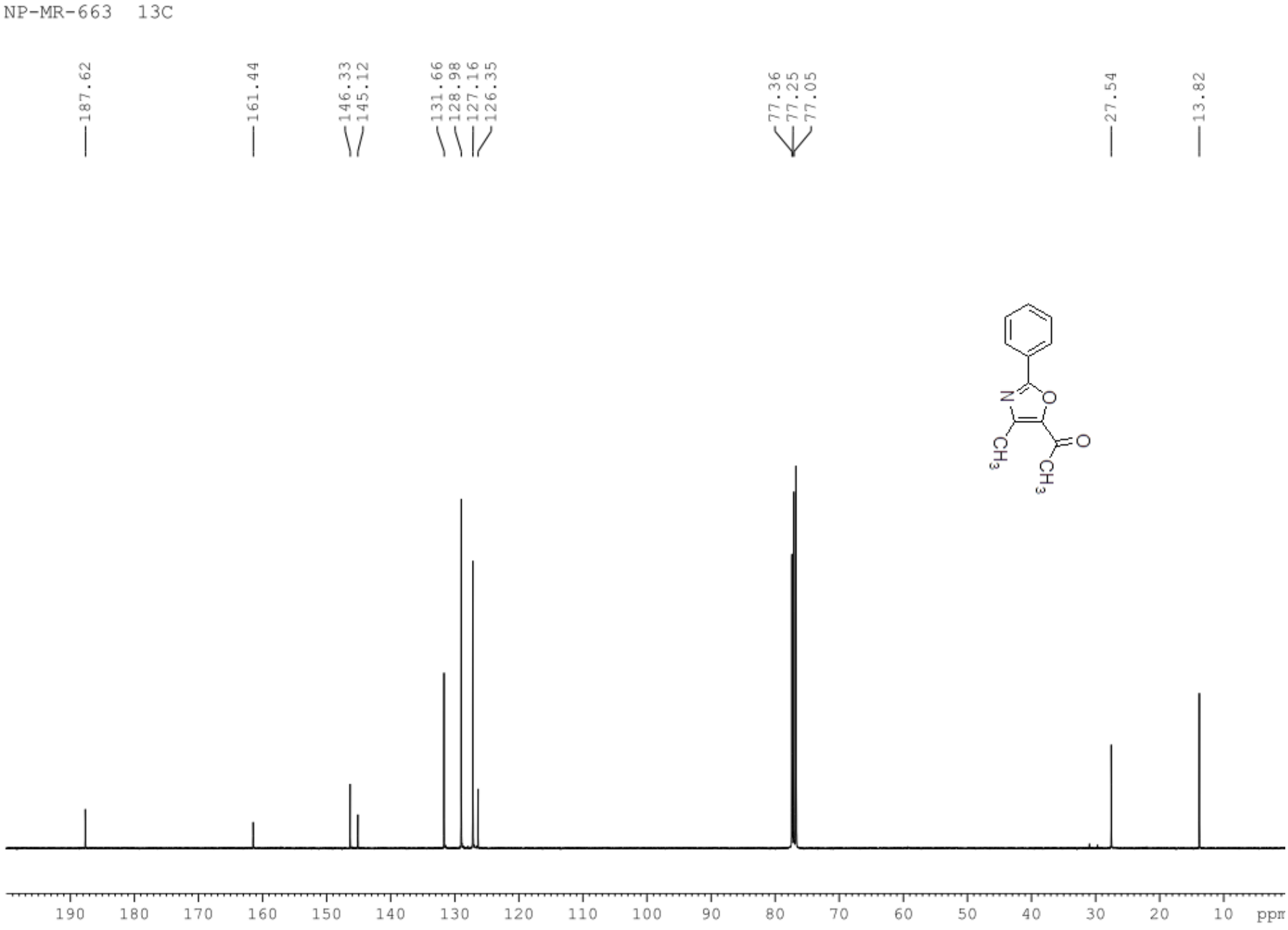
NP-MR-Thioxazole 1H



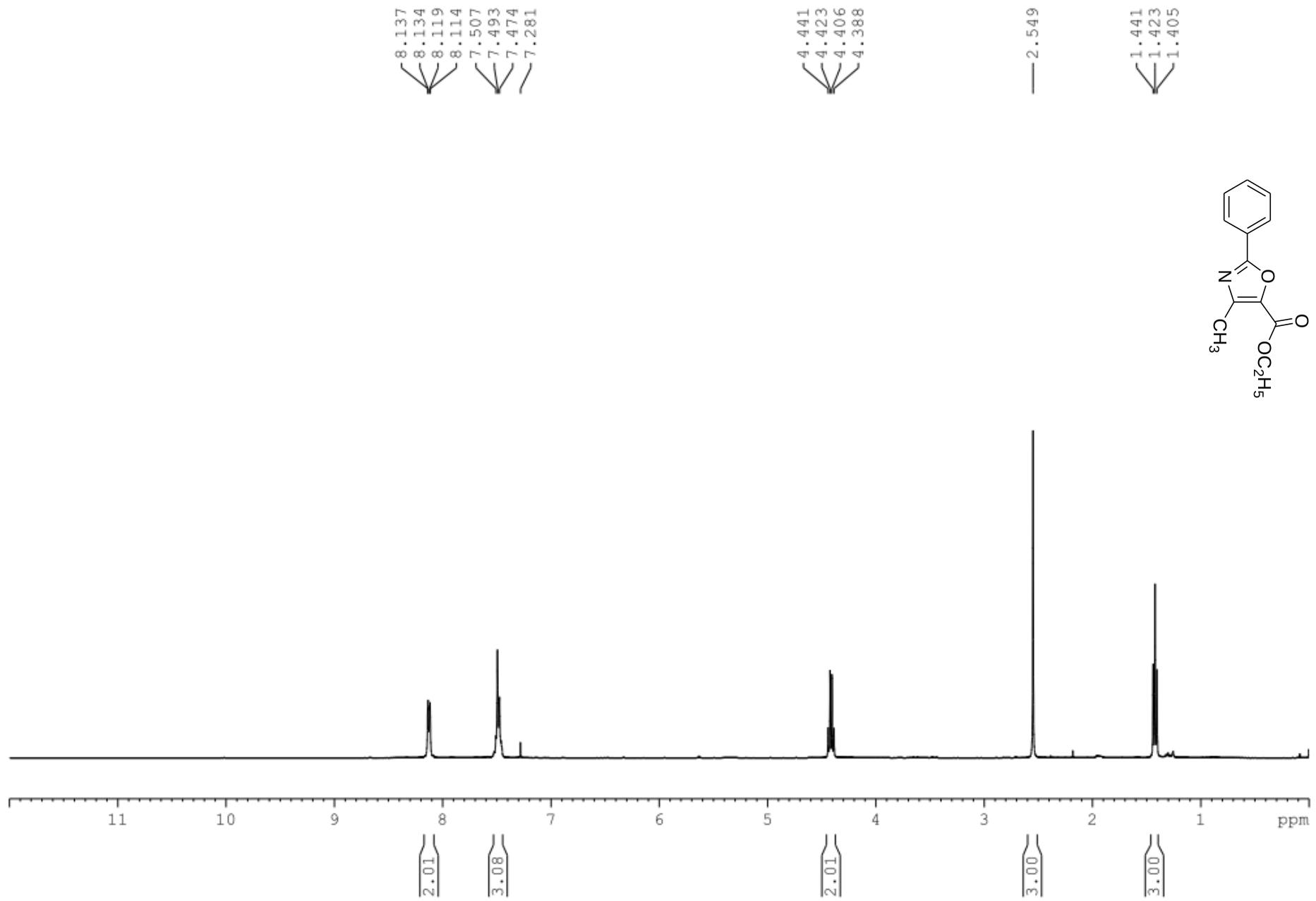

NP-MR-Thiocarbzole -R 13C
173.51
161.87
149.36
132.88
131.28
129.18
128.54
126.92
77.37
77.05
76.73
52.55
O
S
N
OCH3
ppm

NP-MR-663 1H

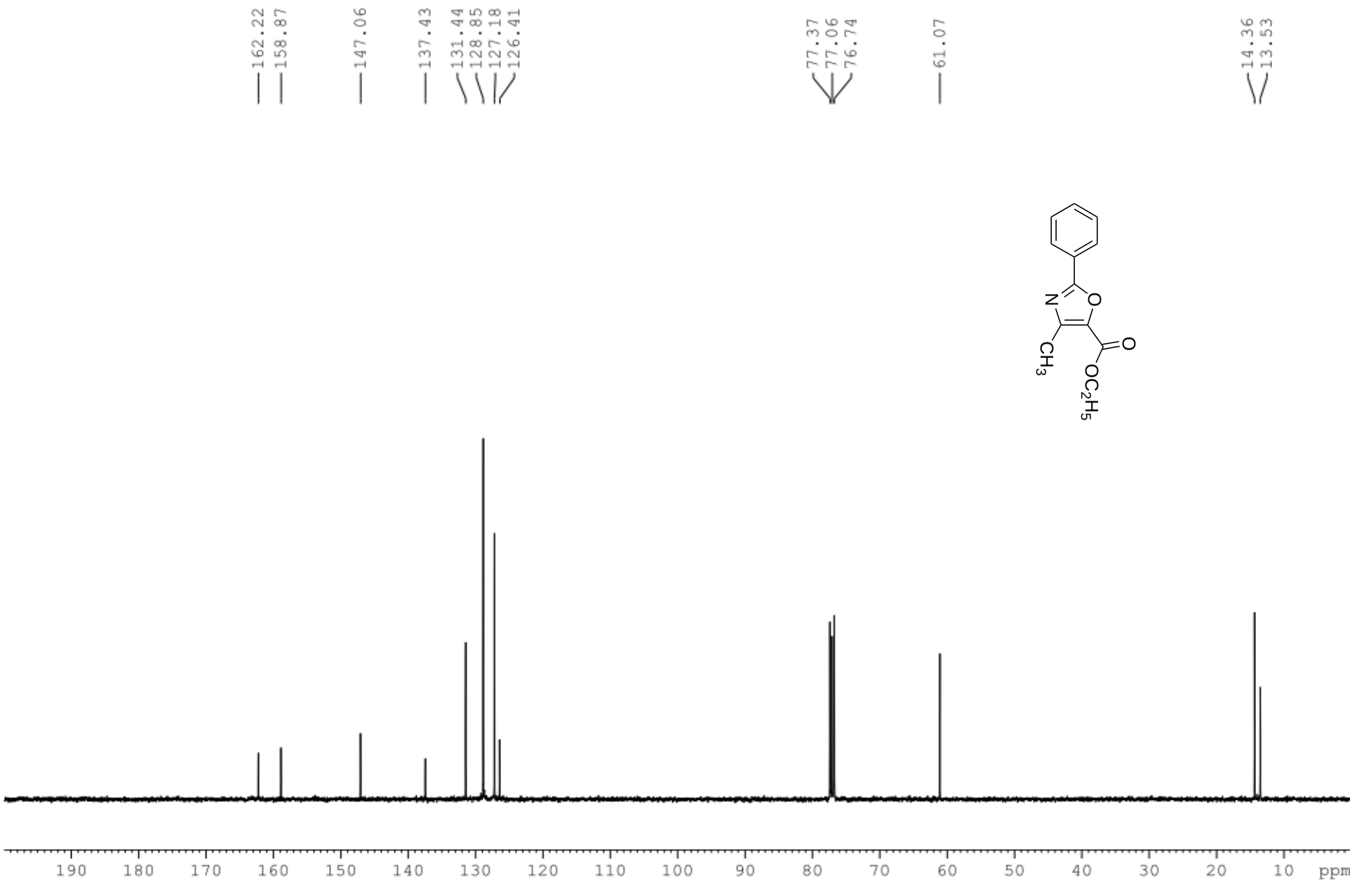

8.135
8.131
8.120
8.116
8.111
7.545
7.537
7.533
7.526
7.515
7.507
7.496
7.492
7.486
7.281
2.583
2.576
N
O
CH3
O
CH3
10
9
8
7
6
5
4
3
2
1
ppm
2.00
3.07
6.14


NP-MR-663 13C
187.62
161.44
146.33
145.12
131.66
128.98
127.16
126.35
77.36
77.25
77.05
27.54
13.82
N
O
CH3
O
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

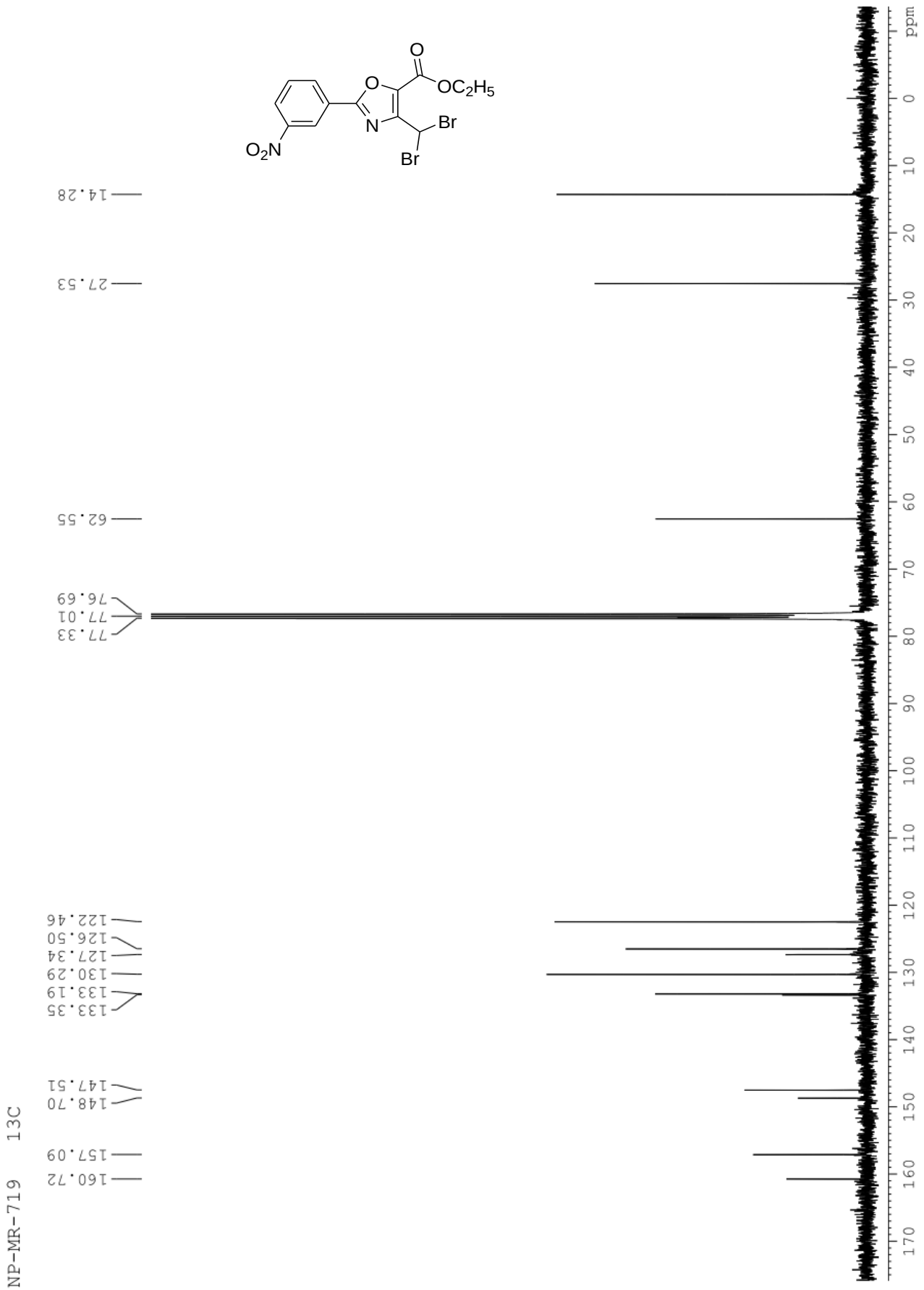
NP-MR-EAA Oxazole 1H



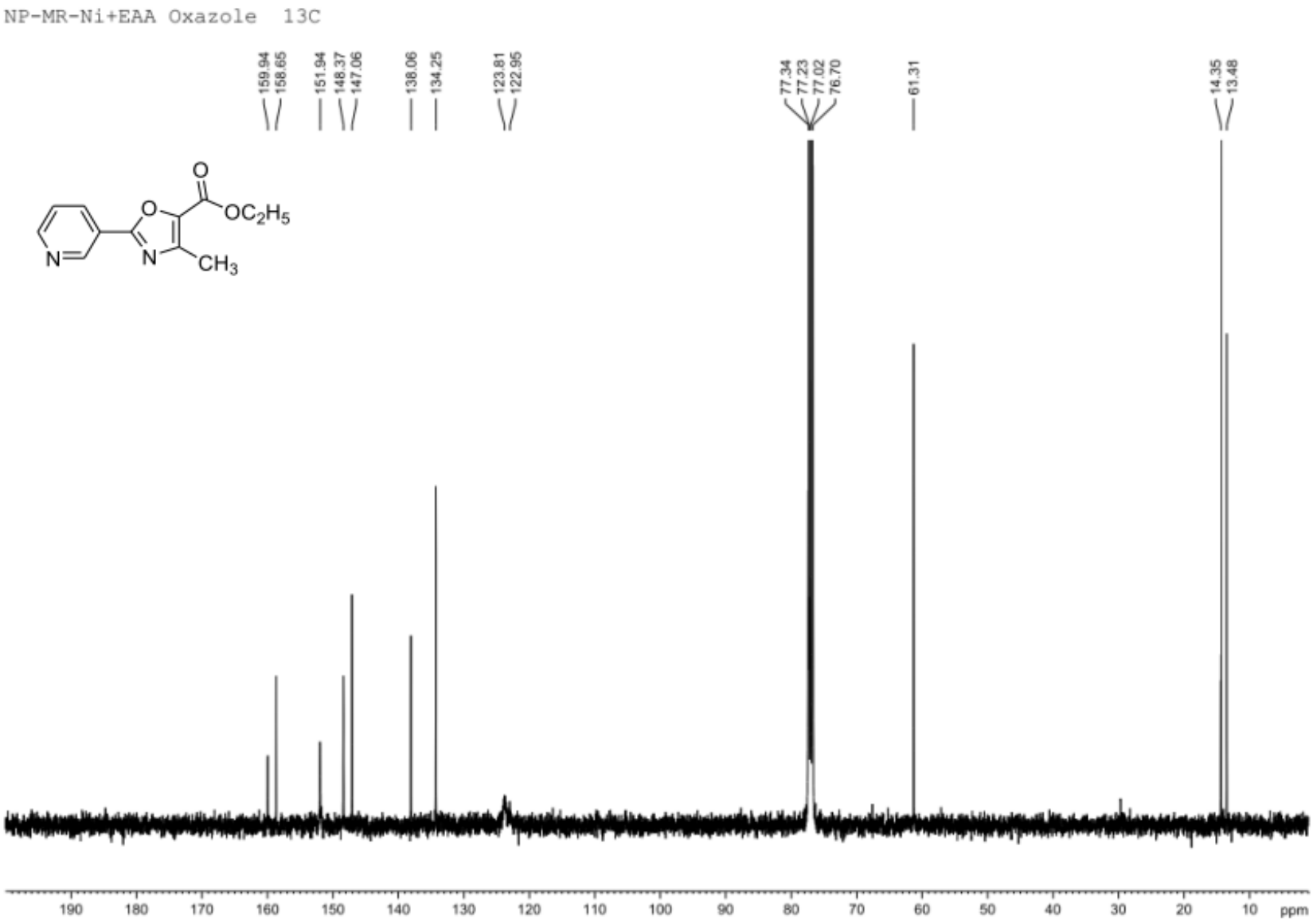
NP-MR-EAA Oxazole 13C



NP-MR-719 1H
1.480
1.497
1.515
4.497
4.514
4.532
4.550
7.282
7.320
7.739
7.759
7.779
8.426
8.428
8.431
8.448
8.451
8.454
8.567
8.584
8.586
9.041
9.046
9.050
O
O
OC2H5
N
Br
Br
O2N
3.19
2.13
0.96
1.11
1.01
1.04
0.91
ppm


O
OC2H5
O
N
Br
Br
O2N
14.28
27.53
62.55
76.69
77.01
77.33
122.46
126.50
127.34
130.29
133.19
133.35
147.51
148.70
157.09
160.72
NP-MR-719 13C
ppm

NP-MR-Ni+EAA Oxazole 1H
9.400
8.792
8.412
8.392
7.464
7.282
4.468
4.450
4.432
4.414
2.574
1.726
1.461
1.443
1.425
1.01
0.98
1.05
1.00
2.07
3.06
3.10
ppm
S56


NP-MR-Ni+EAA Oxazole 13C
159.94
158.65
151.94
148.37
147.06
138.06
134.25
123.81
122.95
77.34
77.23
77.02
76.70
61.31
14.35
13.48
O
O
OC2H5
N
N
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Part - II

Chapter 5

Enol Esters in Organic Synthesis: A Brief Overview

5.1 Introduction

Oxygen analogue of enamide may be called as 'enol ester' motif is abundant in various biological active natural products such as Sebestenoids A–D,[1]Vibsanins B and Neovibsanin B (Fig 1).[2] Additionally, enol esters are used as versatile synthon for numerous reactions such as cycloadditions,[3] Aldol reactions,[4] Mannich type reactions,[5] asymmetric hydrogenations[6] reactions (Scheme 1). Enol esters are also found application in the cyclization reactions to afford chromones,[7] synthesis of amino alcohols[8] as well as polymer synthesis.[9] Enol esters also useful in the acylation of alcohols and amines.[10]

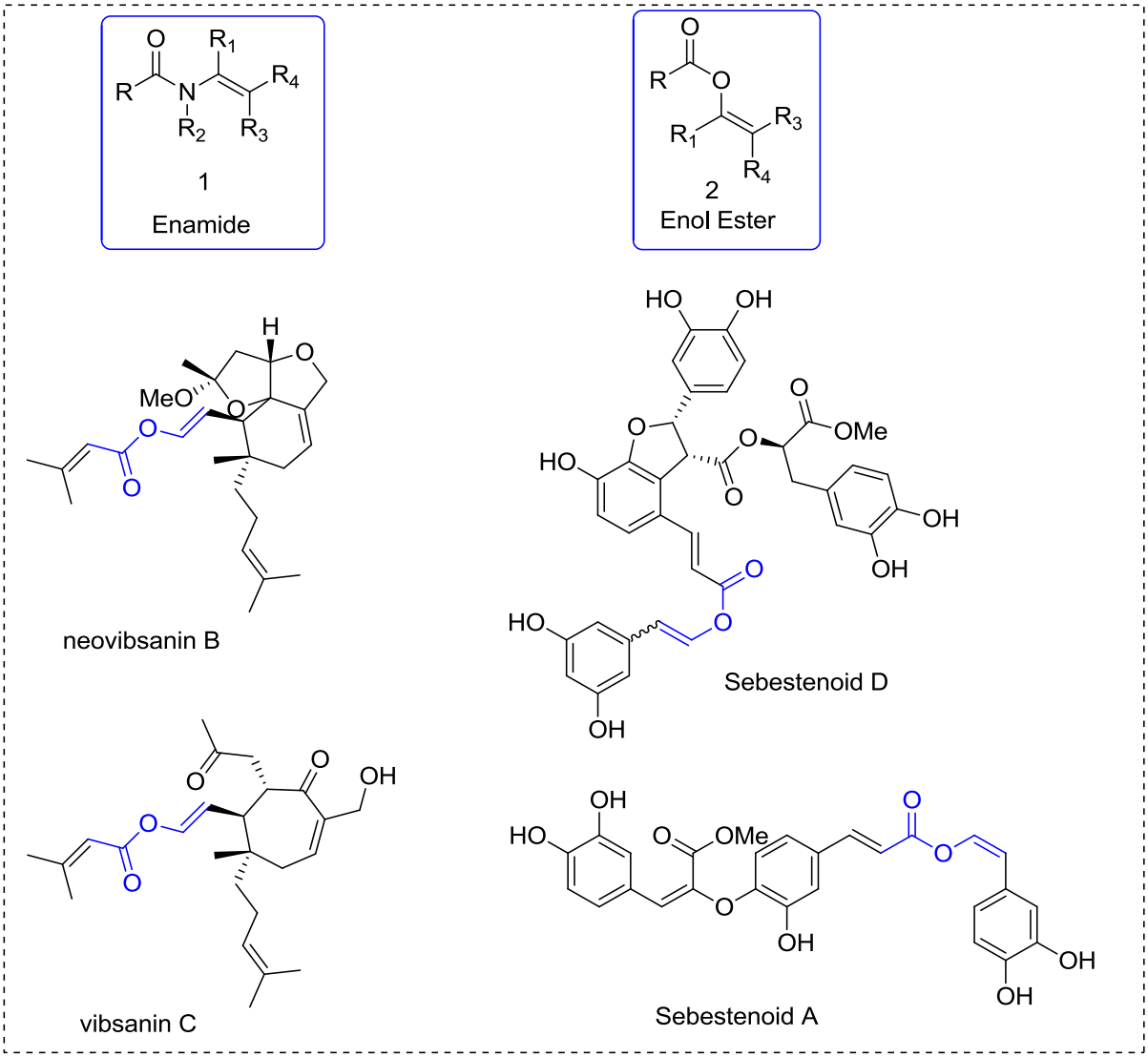
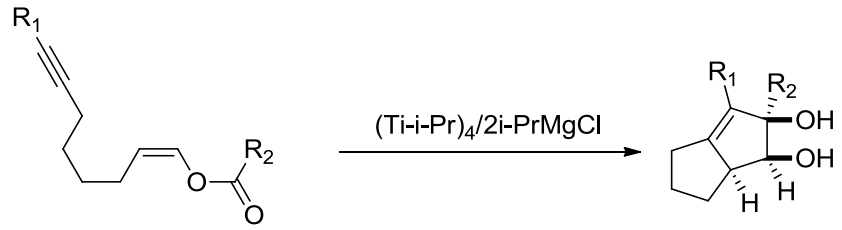


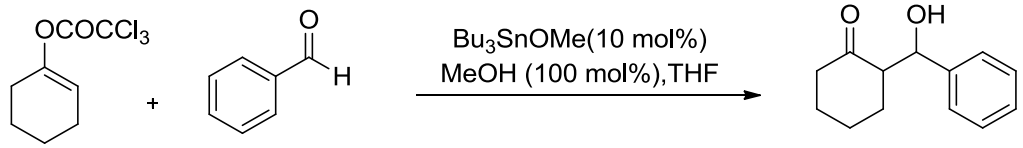
Fig 1: Biologically potent enol esters

Scheme 1: Reactions of enol-esters

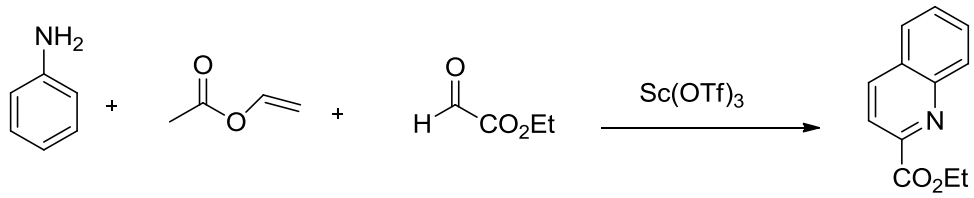
a)Cycloaddition reaction



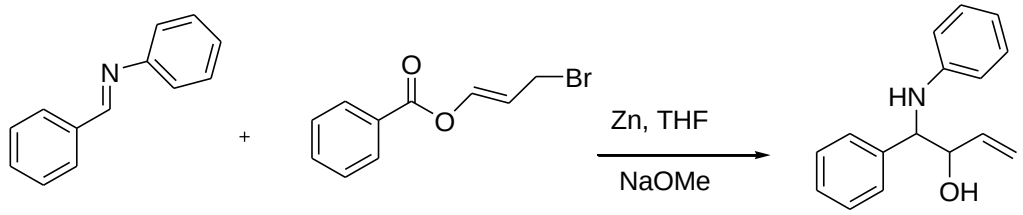
b)Aldol reaction



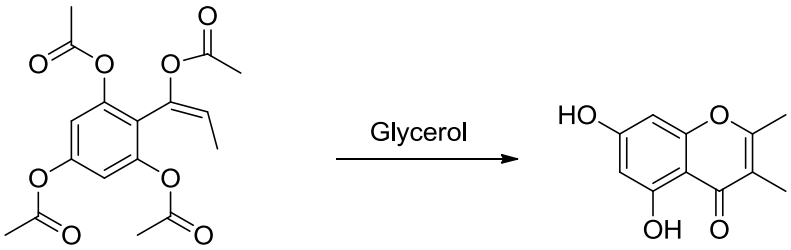
c) Mannich type reaction



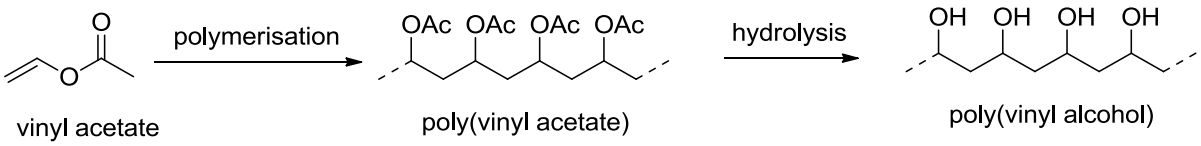
d)Synthesis of Vicinal amino alcohols



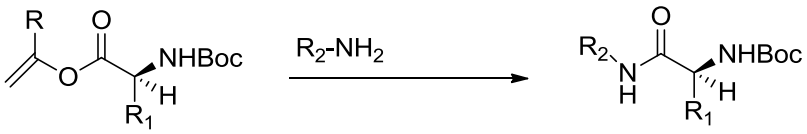
e) Chromone synthesis



f)Polymer synthesis



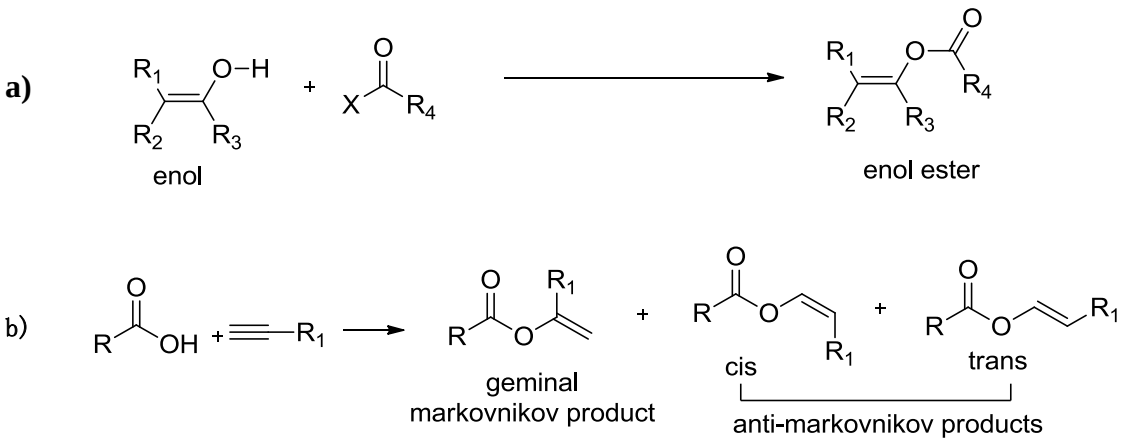
g)Acylation of amine



5.2. Synthesis of Enol Esters

Traditional methods of enol-ester synthesis rely on the acylation of enols/enolates. However, C-acylation is a competitive reaction to *O*-acylation process (Scheme 2). Hence, in order to achieve the enol-esters regioselectively, the addition of carboxylic acid (O-H) to alkyne is an obvious choice. Moreover, such addition reaction in the presence of transition metal catalyst is an efficient and atom-economic method for the synthesis of 1-alkenyl esters. The addition reaction often affords a mixture of three possible 1-alkenyl esters i.e. one Markonikov-type product and two anti-Markonikov-type products with *E* and *Z* geometry (Scheme 2b). Therefore, transition metal catalyzed C-O bond formation leading to enol-ester with high regio- and stereoselectivity has been drawing increasing attention in recent years.

Scheme 2. Synthesis of enol esters

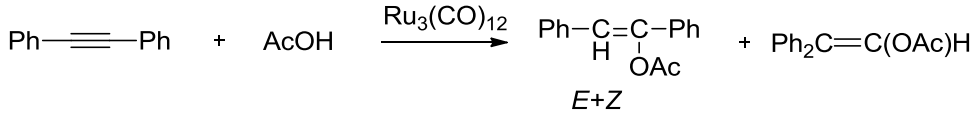


In this regard, several methods have been developed so far. In 1983, Rotem and co-worker first reported the example of the addition of carboxylic acid to alkynes in the presence of $Ru_3(CO)_{12}$ to form mixture of *E* and *Z*-enol estes (Scheme 3a). The addition of unsaturated carboxylic acids to terminal acetylenes in the presence of a catalytic amount of bis(η^5-cyclooctadieny1)ruthenium-P-n-Bu_3 leading to enol esters with high regioselectivity was reported by Watanabe and co-workers (Scheme 3b). In 1995, Dixneuf developed the anti-Markoniv's addition of carboxylic acid with terminal alkynes (aryl acetylene) in the presence of sterically crowded ruthenium catalyst to produce *Z*-enol-esters selectively (Scheme 3c).[11]

Recently, Wada and co-workers developed the ligand-mediated addition of carboxylic acid to terminal alkynes to produce regioselective enol-esters the presence of Ru-catalyst. (Scheme 3d).[12] They prepared active ruthenium catalyst using CeO_2 and phosphine under hydrogen atmosphere. They demonstrated that the Ru-catalyzed addition in the presence of 1,4-bis(diphenylphosphine)butane leads to the anti-Markovnikov adduct whereas reaction in the presence of trioctylphophine gives the Markovnikov adduct. More recently, Wong et al. used a dinuclear ruthenium catalyst for the addition of aliphatic carboxylic acids to phenyl acetylene (Scheme 3e) in the presence of dipyridylamine ligands.[13]

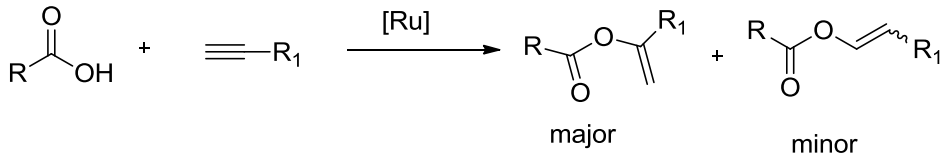
Scheme 3

a)



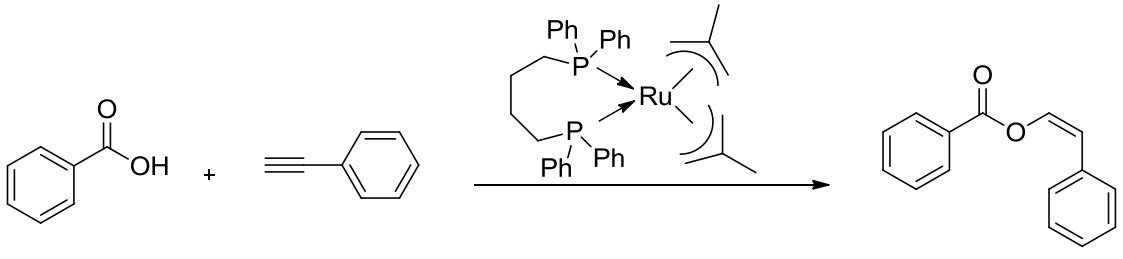
Rotem et al.

b)



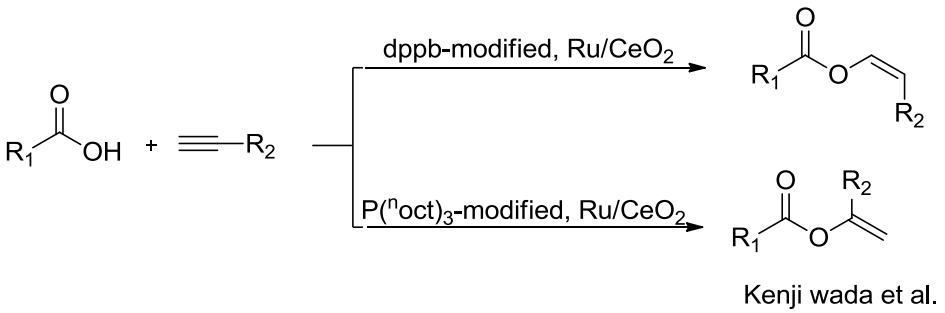
Watanabe et al.

c)

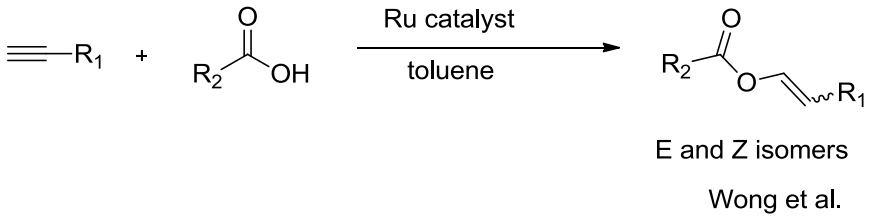


Dixneuf et al.

d)

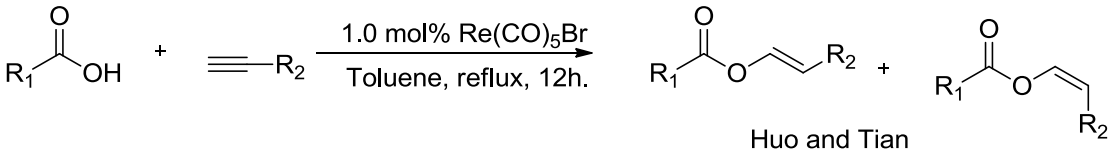


e)



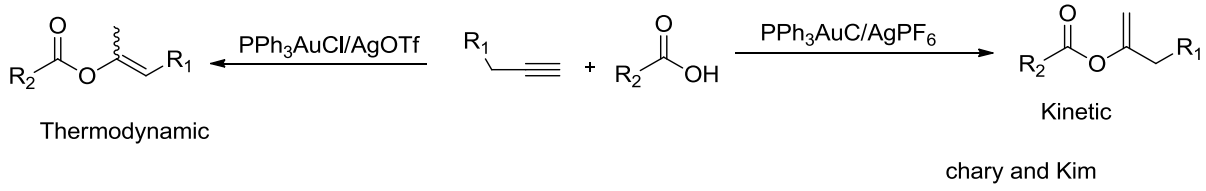
Other transition metal catalysts were also employed for the atom-economic addition reaction to produce enol-esters. For instance, in 2004, Huo and Tian used commercial available rhenium catalyst $Re(CO)_5Br$ for the addition of carboxylic acids to terminal alkynes to afford the mixture of anti-Markovnikov adducts in good yield (Scheme 4).[14] They recovered the catalyst after completion of the reaction and reused successfully with consisted yield of the product.

Scheme 4



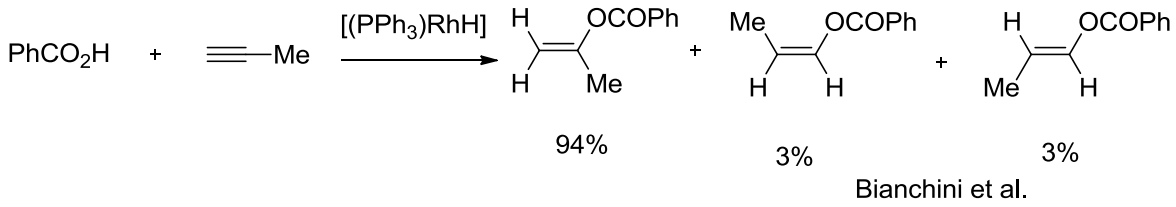
Besides, Chary and Kim applied gold-catalyst to generate enol esters with variable stereoselectivity (Scheme 5).[15a] For instance, when PPh_3AuCl was used with $AgPF_6$, the addition reaction provides the Markovnikov addition products, whereas, in the presence of AgOTf the more stable isomerized Markovnikov-type addition product resulted (Scheme 5).

Scheme 5



Rh(I) monohydride complex was also used by Bianchini et al.[15b] for the synthesis of enol esters with high regioselectivity (Scheme 6).

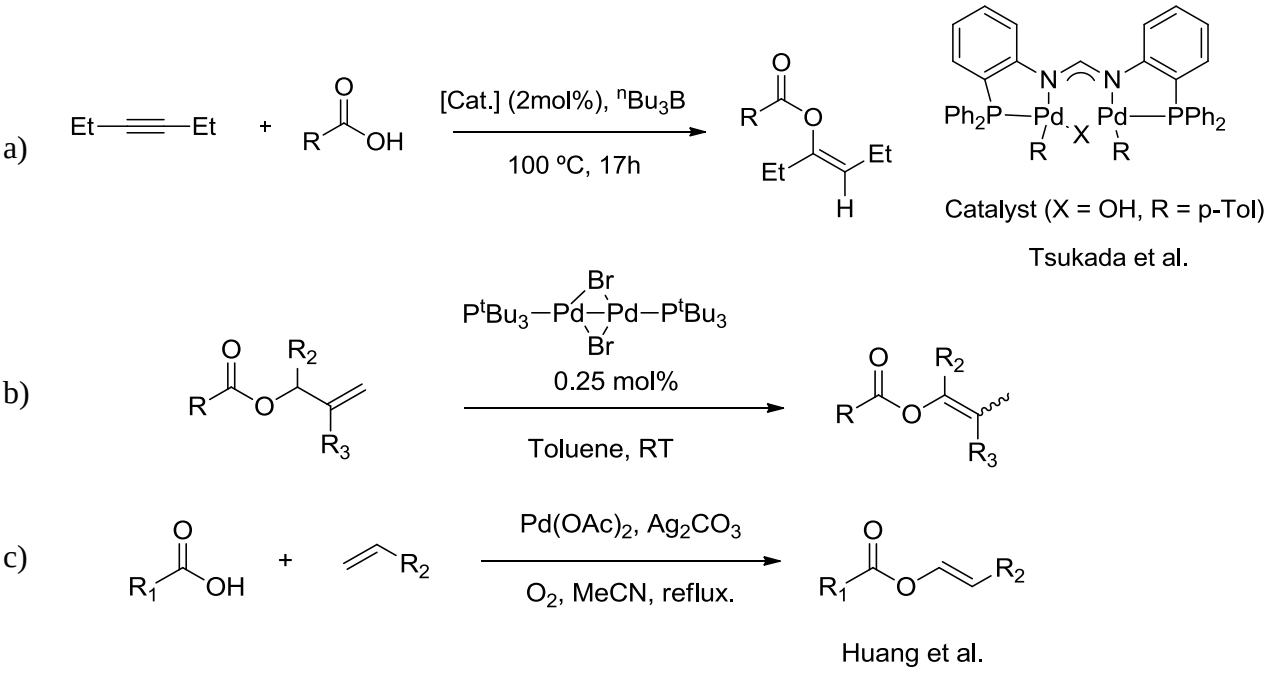
Scheme 6



Bianchini et al.

Tsukada et al. reported dinuclear palladium complex catalyzed addition of carboxylic acids to unactivated internal alkynes to afford trans-adduct selectively (Scheme 7a).[16] Gooßen et al. also described the dimeric Pd(I)-complex catalyzed synthesis of enol esters from allylic esters (Scheme 7b).[17] In a recent literature, Huang and co-workers used alkenes for the successful coupling with carboxylic acids in the presence of Pd-catalyst (Scheme 7c).[18] This methodology is a complementary method to the addition of carboxylic acids to alkynes.

Scheme 7



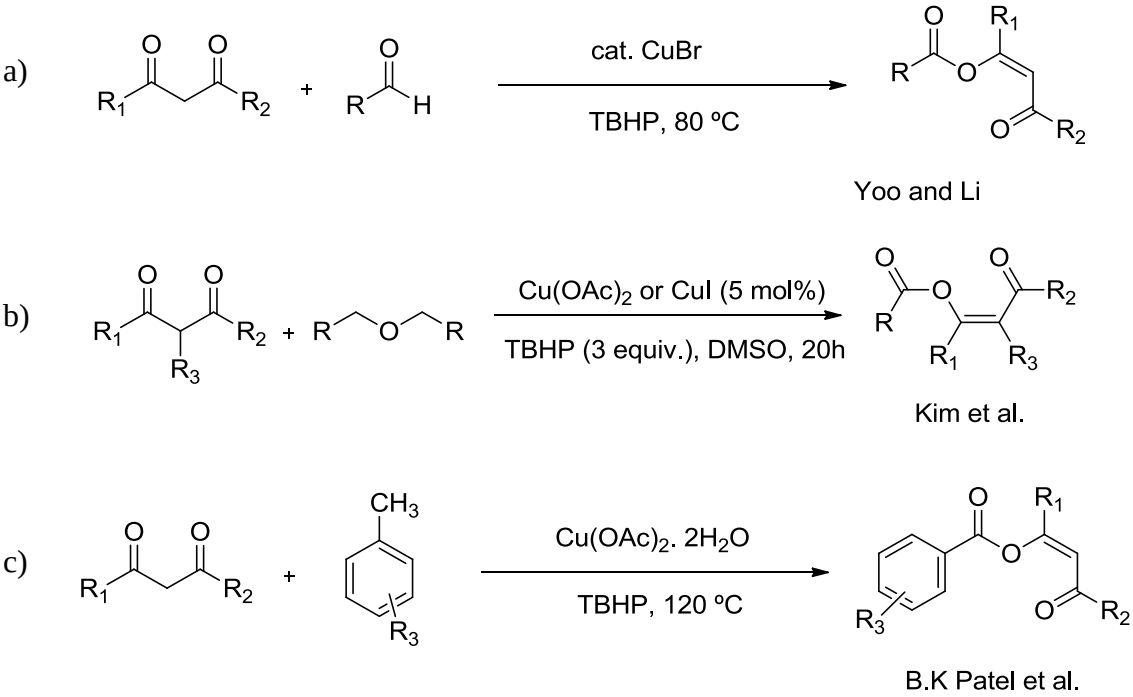
Tsukada et al.

Huang et al.

Apart from carboxylic acid addition reaction, 1,3-dicarbonyl compounds are also used as a precursor to obtaining enol esters. For example, in 2006, Yoo and Li developed the copper(I) bromide catalyzed oxidative esterification reaction of aldehydes with β-dicarbonyl compounds using TBHP as an oxidant to afford the enol esters in good yields (Scheme 8a).[19]Very recently, Patel et al. described copper catalyzed esterification of alkyl benzene

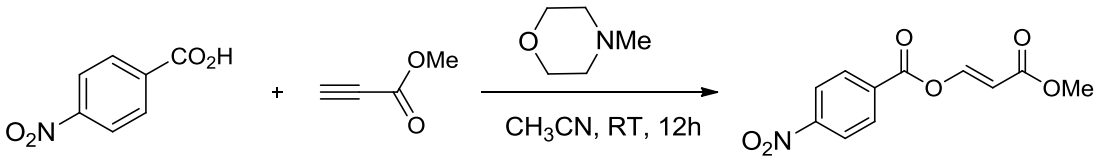
using β-dicarbonyl compound in the presence of TBHP oxidant to produce enol esters in good yield (Scheme 8b).[20] Most recently, Kim group reported a similar efficient strategy for the synthesis of enol esters using copper-catalyzed oxidative coupling of 1,3-dicarbonyl compounds with dialkyl ethers or dibenzyl ethers in the presence of TBHP (Scheme 8c).[21]

Scheme 8



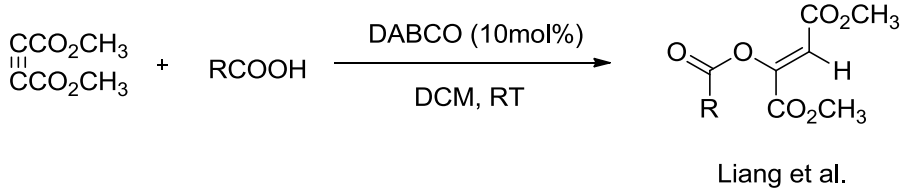
Besides, progress has been made on the metal-free addition of carboxylic acid with the electron deficient alkynes in the presence of a base. Interestingly, Ryu et al. used 4-methyl morpholine mediated synthesis of enol ester from the reaction of *p*-nitro benzoic acid and alkyl propiolate in polar solvent (Scheme 9).[22]

Scheme 9



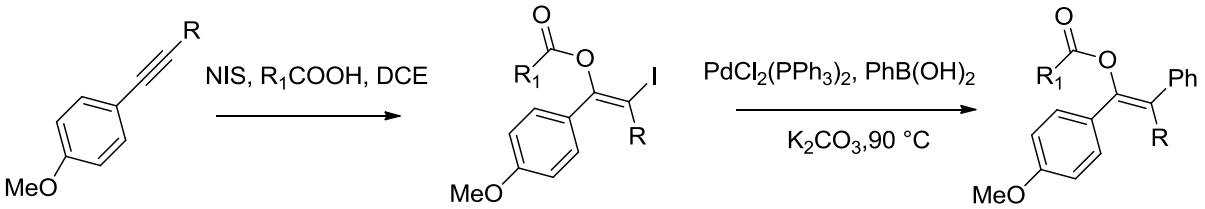
In 2006, Liang and co-workers described, 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed addition of carboxylic acids to activated alkynes to form substituted enol esters in good yield (Scheme 10).[23]

Scheme 10



In 2011, Yanada et al. developed a regio- and stereoselective synthesis of enol-ester with co-halogenation from alkynylbenzenes (Scheme 11). The stereoselectivity of the reaction is dependent upon the substituent on the acetylene terminus. Alkyl-substituted alkynyl benzene proceeded via anti-addition, affording *E*-iodoalkene while aryl-substituted alkynylbenzene exhibited a preference for syn-selectivity. The resulting iodoalkene was utilized for the transformation through a Pd-catalyzed coupling reaction. A one-pot regio and stereoselective cohalogenation/Suzuki-coupling reaction were also achieved.

Scheme 11



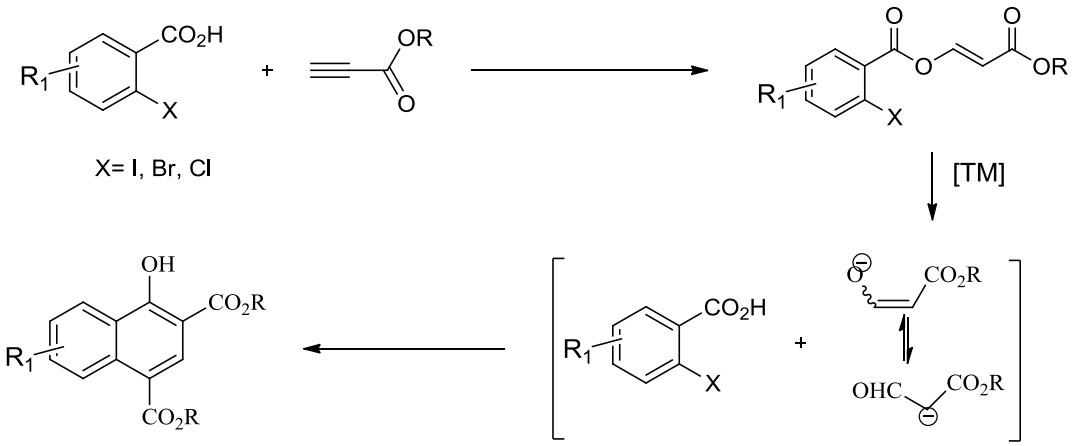
Yanada et al.

5.3 Objectives

Considering the recent progress on enol ester synthesis and their applications, we conceived that addition of aryl carboxylic acid to electron deficient alkynes is a convenient and easy approach to achieving the corresponding enol esters. Induction of a functional group such as halogen to the aromatic ring might open the opportunity for annulations reactions. At the onset, our objectives were (Scheme 12):

- To prepare the enol esters of *ortho*-halo benzoic acid
- Use of enol esters of ortho-halogenyl carboxylic acid for the unprecedented synthesis of naphthols.

Scheme 12



Our effort in this context is presented in chapter 6.

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Chapter 6

Synthesis of α-Naphthols from Enol Esters

6.1 Introduction

Naphthalene derivatives are found abundantly in various natural products such as Rubicordifoline, mollugin, Nigerone, *cis*-hydroxymollugin etc (Figure 1). Naphthalenes also show important biological properties such as antimalarial,[1] anti-HIV and anticancer activities.[2] They are also found applications in agrochemical and dye preparations.[3]Apart from this, naphthols, the most important naphthalene derivatives serve as versatile chiral ligands in synthetic organic chemistry.[4]

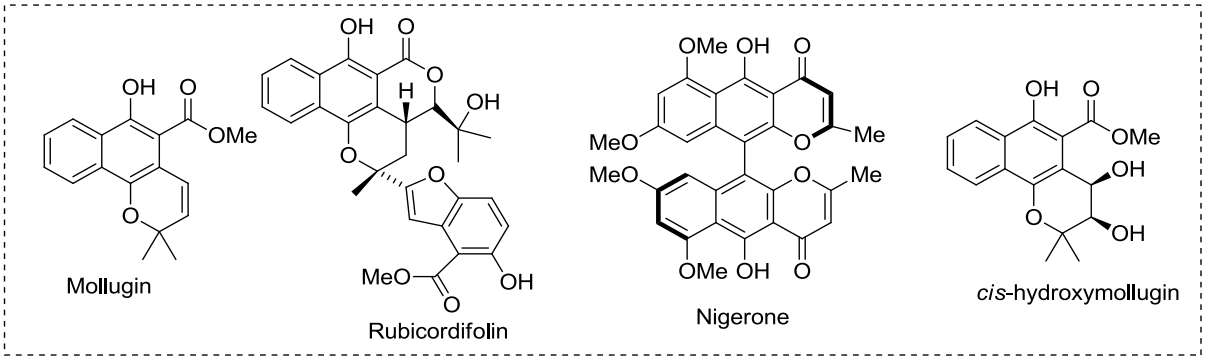


Fig 1: Biologically important naphthol derivatives

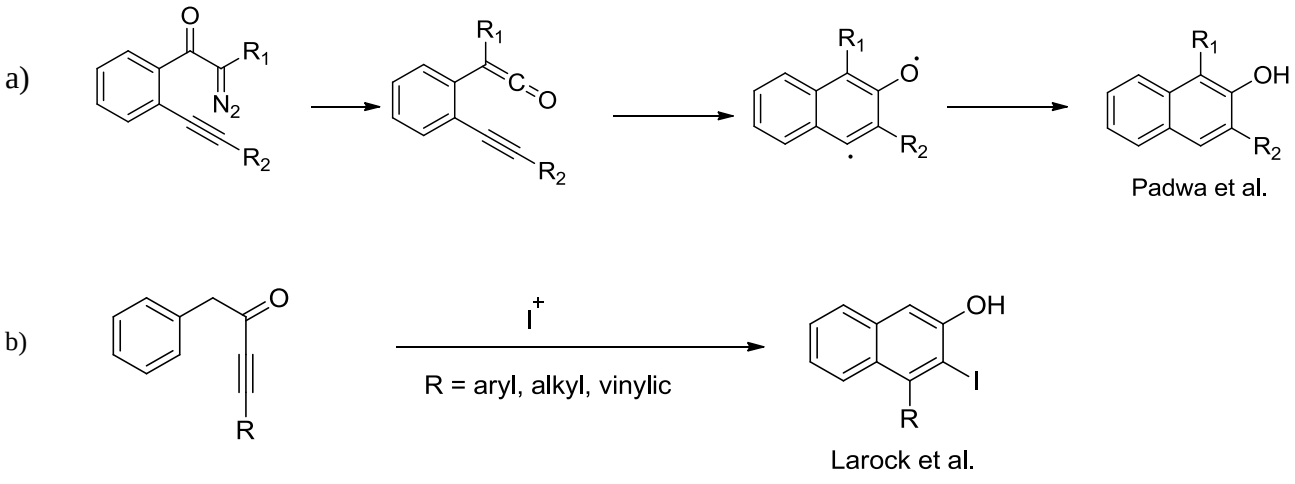
The profound usage of naphthalene derivatives particularly, naphthols stimulates the development of new and complementary methods for their synthesis. Stepwise electrophilic aromatic substitution to a naphthalene ring is recognized as a conventional method to access polysubstituted naphthalenes by functionalization of aromatic C-H bonds to C-C and C-N/O bonds. Complex reaction conditions and frequent formation of regioisomeric mixtures are the inevitable drawbacks associated with the above process.[5] Thus, a number of eminent methods including the Diels–Alder reaction, Hauser phthalide annulations,[6] rearrangement of cyclopropanes or cyclobutanes, and acid-catalyzed cyclization reactions have been developed.[7] Numerous transition metal catalysts encompassing Cr, Mn, Pd, Rh, and Cu were also successfully employed for the construction of naphthalene rings from their monocyclic precursors owing to their advantages over the regioselectivity problem.[8] In contrast, the regioselective synthesis of naphthols with predetermined substituents is less well endowed with literature precedents. Some elegant methods of naphthol synthesis are presented below.

Notably, in 1993, Padwa and co-workers demonstrated that the synthesis of poly substituted naphthols from the photolysis of β-diazopropiophenone derivatives (Scheme 1a).[9]

In 2006, Larock et al. used mild reaction conditions for the synthesis of 3-Iodo-2-naphthols by the cyclization of 1-aryl-3-alkyn-2-ones (Scheme 1b). This reaction proceeds only in the presence of electrophiles such as ICl, I_2, and NBS.[10] In 2007, another interesting method for the construction of naphthols has been developed by Huang and Jian. They carried out the multi-component reaction of arynes, β-keto sulfones and Michael-type accepters (Scheme 1c)[11] to achieve substituted α-naphthols. In 2010, Jiang group developed mild reaction conditions for the synthesis of multi substituted naphthols using copper catalyst (Scheme 1d).[12]Wirth and his coworkersalso cyclized the β-keto ester substituted stilbene derivatives to naphthol derivatives in the presence of iron catalyst (Scheme 1e).[13]

In 2011, Feng and co-workers used carbonylative Stille coupling reaction of 2-bromobenzyl bromides with tributylallylstannane and subsequent intramolecular Heck reaction to afford 2-naphthols in good yield (Scheme 1f).[14] Interestingly, base catalyzed reaction of benzyne intermediate with 1,3-dicarbonyl compounds leading to 2-naphthol derivatives was reported by Okuma and co-workers (Scheme 1g).[15] In 2012, Youn et al. prepared substituted naphthols by utilizing the palladium catalyzed reaction of 2-alkenylphenyl β -ketoesters and 1,3-diketones with olefins (Scheme 1h).[16]Recently, Wang and co-workers developed anefficient route to polysubstituted naphtholsfrom the intramolecular formal diazo carbon insertion of tosyl hydrazones to keto C-C bonds (Scheme 1i).[17] Photolytic cyclization of electron-deficient bromides with internal alkynes in the presence of Ir-catalyst is also reported to be an interesting method to produce 2-naphthols (Scheme 1j).[18]

Scheme 1



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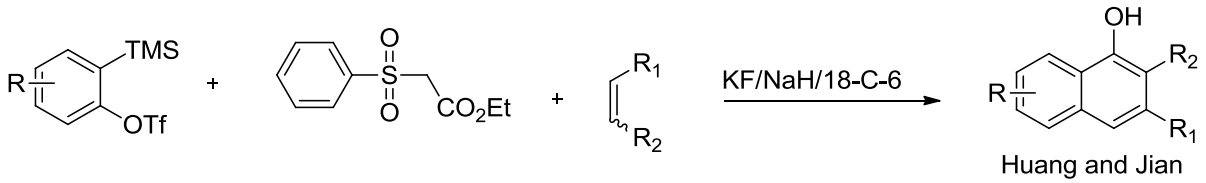
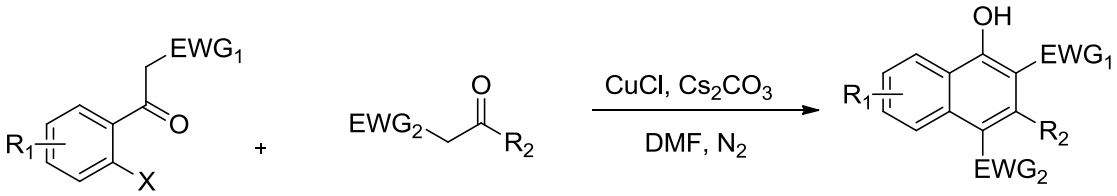


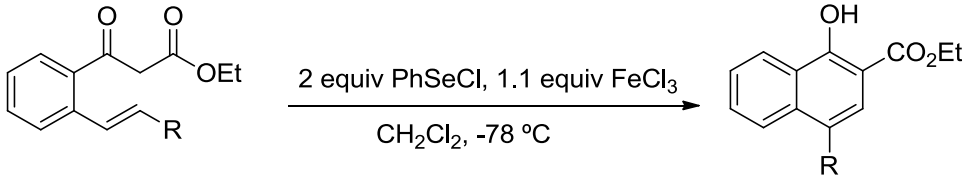
Huang and Jian

d)



Jiang et al.

e)



Wirth et al.

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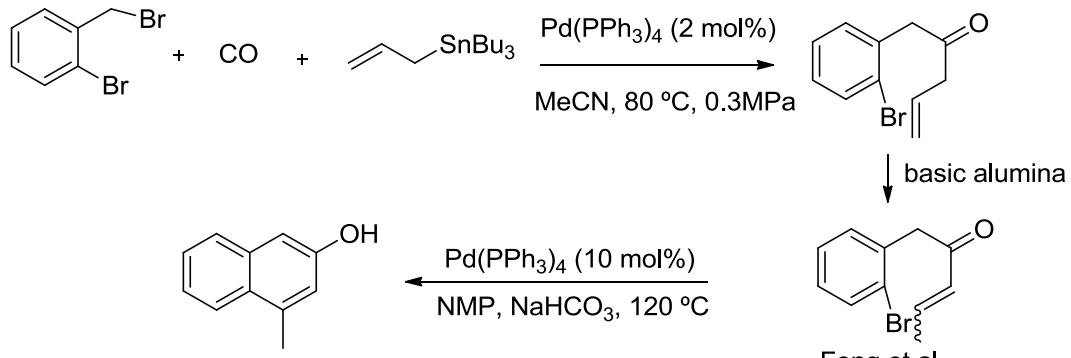
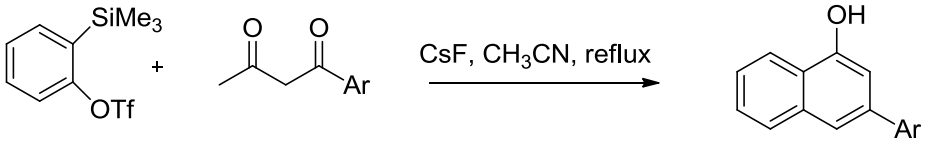


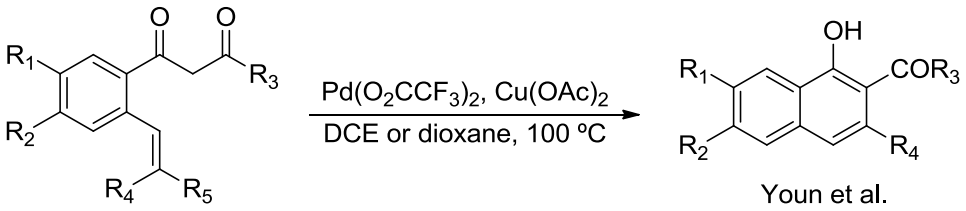
Feng et al.

g)



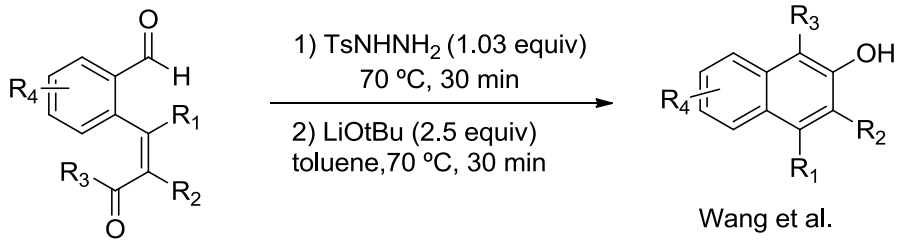
Okuma et al.

h)



Youn et al.

i)



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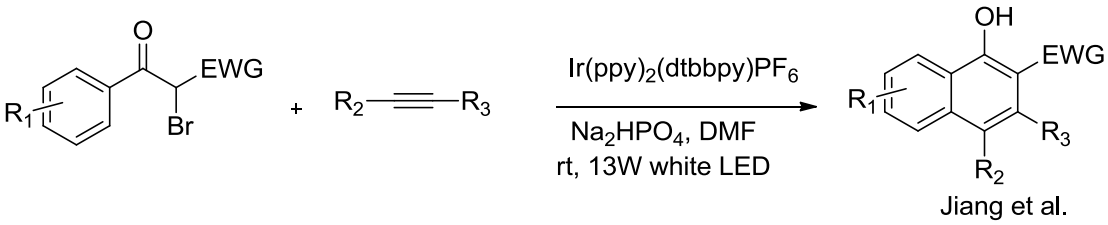
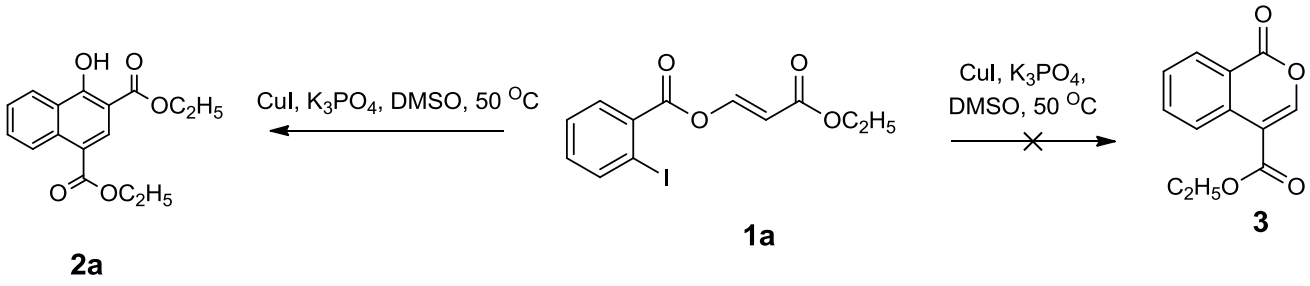


As part of our continued interest on transition metal-catalyzed C-C and C-N bond forming processes, we here disclose a *de novo* copper-catalyzed protocol involving two molecular equivalents of enol esters to produce substituted α-naphthols under mild reaction conditions.

6.2 Results and Discussion

Our work initiated with a serendipitous discovery: on treatment of (*E*)-2-(ethoxycarbonyl)vinyl 2-iodo-benzoate (**1a**) in the presence of a copper salt and base, an intramolecular cyclization to isocoumarin derivative **3** did not occur, rather a new product with a molecular weight of 288 (as shown by the ESI-MS) was produced predominantly (Scheme 2). The product was purified and an attempt was made to characterize it by NMR spectroscopy. The NMR data shows a phenolic proton giving a singlet at 12.52 ppm, which gradually disappears on treatment with D_2O by deuterium exchange. The appearance of distinguishing signals for ethyl groups indicates the presence of two ethyl ester substituents in the new product. In consideration of the ^{1}H and ^{13}C NMR spectra, we anticipated the structure to be that of diethyl 4-hydroxynaphthalene-1,3-dicarboxylate (**2a**).The exact structure of **2a** was further confirmed from X-ray crystallography (Figure 2). See the experimental data for details. This result is completely unprecedented, although encouraging. Thus, efforts have been made to study the feasibility of this novel coupling reaction to access multisubstituted α-naphthols.

Scheme 2



2a **1a** **3**

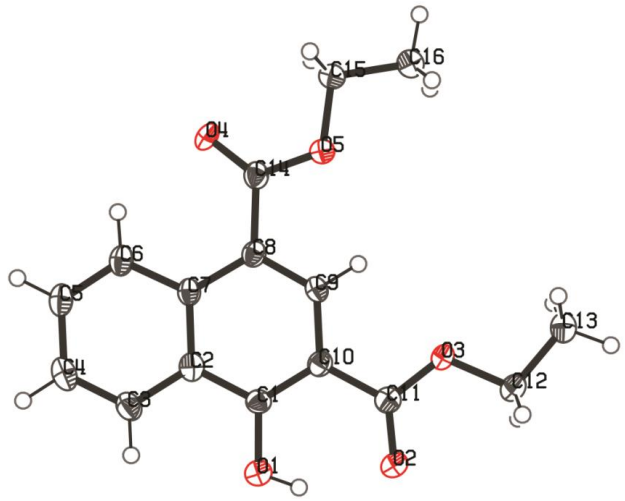
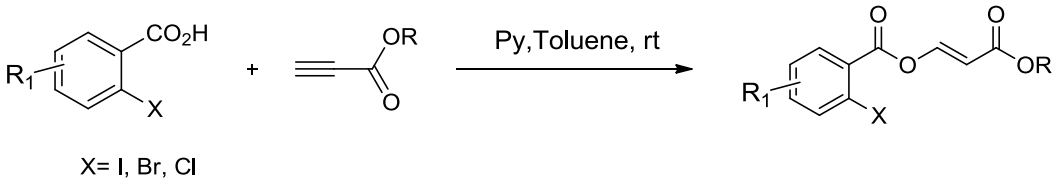


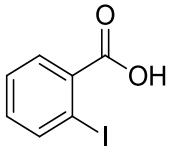
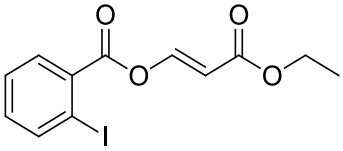
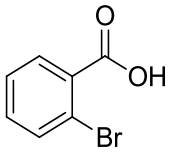
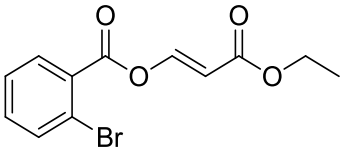
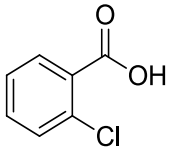
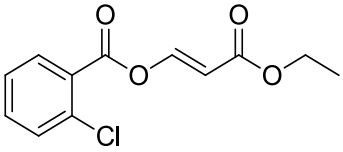
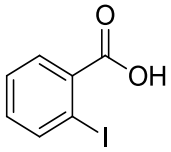
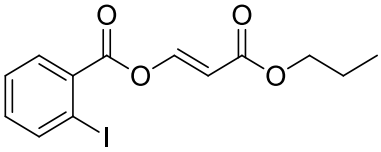
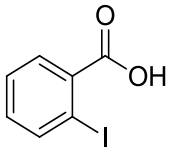
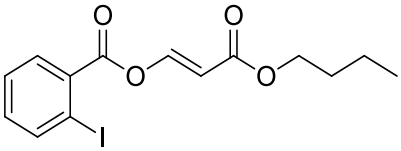
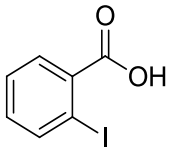
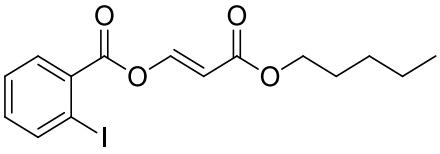
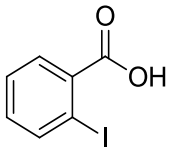
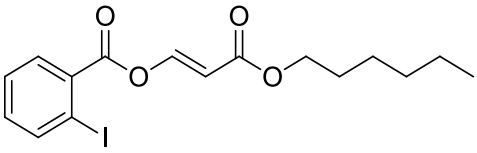
Fig 2: ORTEP drawing of naphthol (**2a**)

To test the feasibility of the process, a number of enol esters were prepared by following a slightly modified method reported by Ryu and his co-workers[19]. For instance, when 2-halobenzoic acid was treated with alkyl propiolate in toluene in the presence of 2 equiv. of pyridine (Table 1), enol ester **1a-p** was produced. Formation of enol ester (**1a**) is evident from IR, NMR as well as MS data. For instance, the IR spectrum shows a strong peak at 1748 cm^{-1} which indicated the presence of ester group. In ^{1}H NMR spectrum, doublets at δ 8.53 and 5.92 with coupling constant 12.4 Hz corresponds to the olefinic protons with *E*-geometry. The presence of a quartet at 4.26 (q, 2H, J = 7.2 Hz) and a triplet at 1.34 (t, 3H, J = 7.2 Hz) confirmed the presence of ester group. In ^{13}CNMR spectra, Presence of twelve line signal confirmed the structure of enol-ester. Molecular composition of **1a** was further confirmed from the mass spectrum, that shows m/z $(M+Na)^{+}$ signal at 369.

Table 1. Synthesis of enolesters[a]



X= I, Br, Cl

Entry	Carboxylic acid	Enol ester	Yield (%)
1		 **1a**	85
2		 **1b**	80
3		 **1c**	83
4		 **1d**	78
5		 **1e**	76
6		 **1f**	72
7			81

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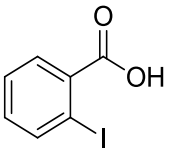
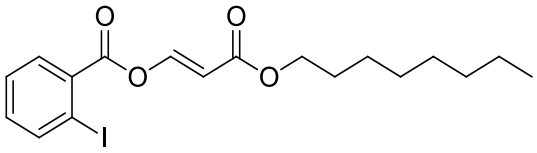
8			85
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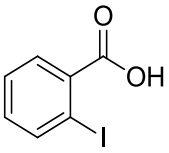
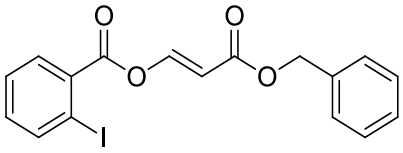
9			80
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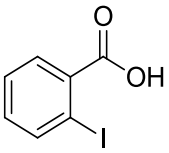
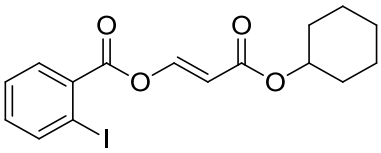
10			73
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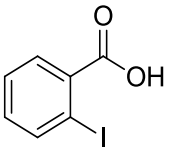
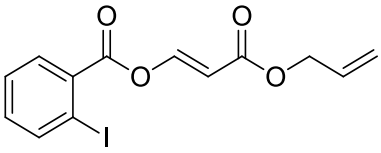
11			71
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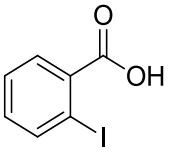
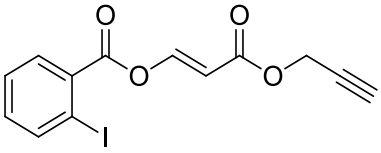
12			76
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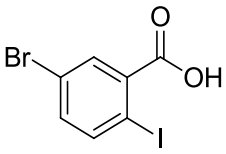
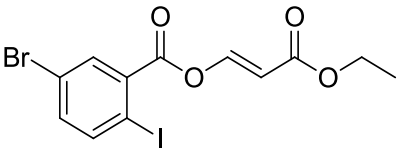
13			79
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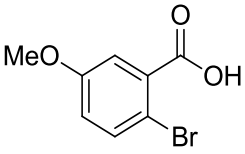
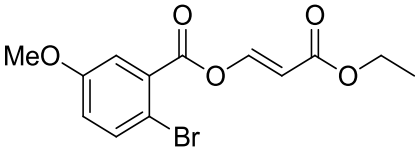
14			72
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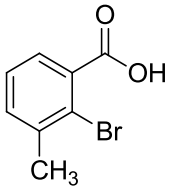
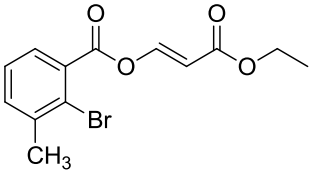
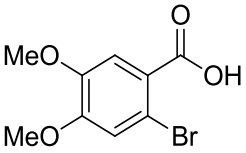
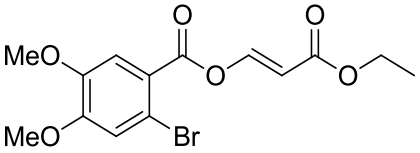
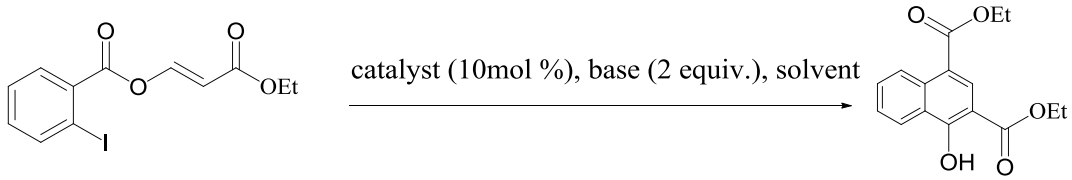
15		 **1o**	70
16		 **1p**	81

[a]*Reaction conditions:*carboxylic acid (1 equiv.), alkyne (1.2 equiv.), pyridine (2 equiv.), toluene, rt, 12h.

Having a number of enol esters, the cyclization reaction was attempted in the presence of copper catalysts. The results are summarized in Table 3. It was observed that, among the tested solvents, the reaction only proceeds in the presence of DMSO and DMF, whereas no naphthol **2a** was isolated in other solvents such as $ClCH_2CH_2Cl$, THF, methanol, 1,4-dioxane and toluene (entries 14–18).

Table 3: Optimization of the reaction conditions



Entry	Catalyst	Base	Solvent	Yield (%)
1	CuI	Cs_2CO_3	DMSO	62
2	CuI	K_2CO_3	DMSO	0
3	CuI	KOAc	DMSO	0
4	CuI	t-BuOK	DMSO	48
5	**CuI**	**K_3PO_4**	**DMSO**	**82**
6	–	K_3PO_4	DMSO	0
7	CuI	–	DMSO	n. r.
8	CuBr	K_3PO_4	DMSO	33
9	$Cu(OAc)_2$	K_3PO_4	DMSO	58
10	$Cu(OTf)_2$	K_3PO_4	DMSO	0
11	CuCl	K_3PO_4	DMSO	43

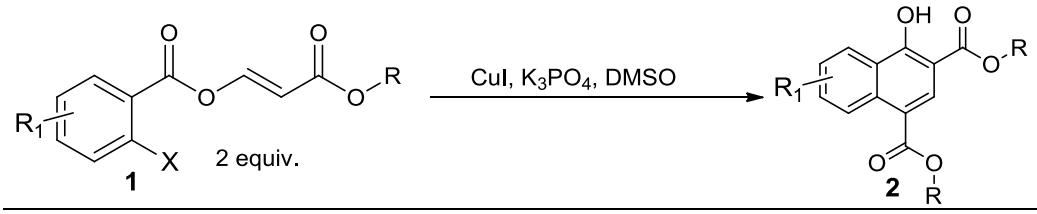
12	CuO	K_3PO_4	DMSO	0
13	CuI	K_3PO_4	DMF	62
14	CuI	K_3PO_4	THF	0
15	CuI	K_3PO_4	1,4-dioxane	0
16	CuI	K_3PO_4	toluene	n.r.
17	CuI	K_3PO_4	$ClCH_2CH_2Cl$	n.r.
18	CuI	K_3PO_4	methanol	0

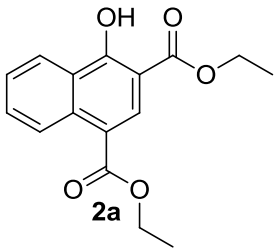
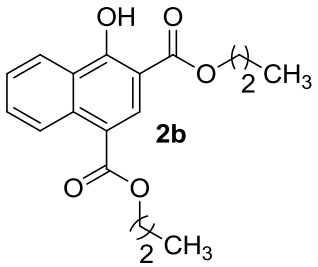
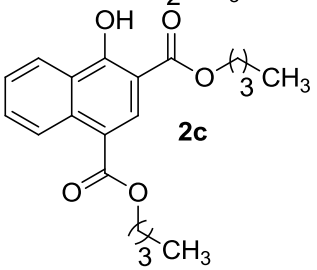
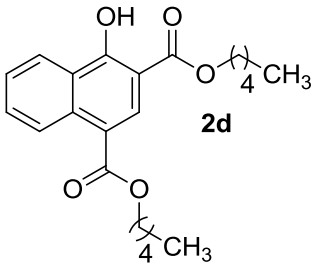
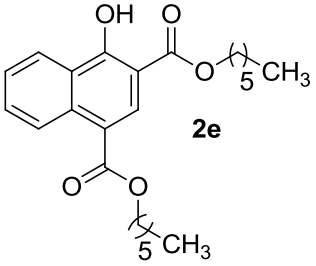
Reaction conditions: enol ester (100 mg, 0.29 mmol), catalyst (10mol %), base (2 equiv.), solvent (3 mL), 50 ºC for 5 h; n.r. represents no reaction

The reactivity of different copper catalysts and bases were also investigated. It was observed that CuI (10 mol%) served as the best catalyst to provide naphthols **2a** in optimum yield (82%). Notably, the yield of the reaction was calculated from the reaction of 2 molar equiv. of enol ester which leading to 1 molar equiv. of naphthol. A decrease in CuI concentration from 10 mol% to 5 mol% afforded the naphthol in poor yield (62%), whereas an increase in catalyst concentration to 20 mol% did not produce better results (75%). Among the tested bases (Cs_2CO_3, K_2CO_3, KOAc, t-BuOK and K_3PO_4), K_3PO_4 provided naphthol **2a** in the highest yield in DMSO at 50 ºC. The concentration of a base is also revealed to be important. Two equivalents of the base were needed to produce the naphthol **2a** in a maximum yield. Lowering the temperature from 50 ºC to room temperature or increasing the temperature to 90 ºC afforded naphthols **2a** with nearly the same yield within 24 h and 2 h, respectively. Importantly, this reaction protocol required neither an anhydrous atmosphere nor extra pure solvent to produce multisubstituted naphthols in good yield.

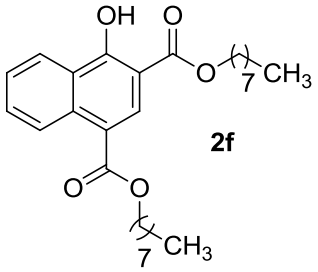
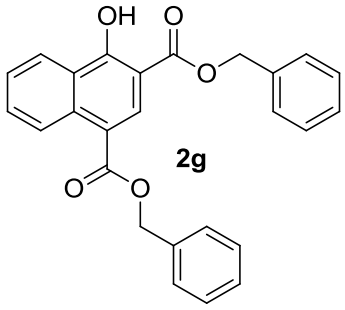
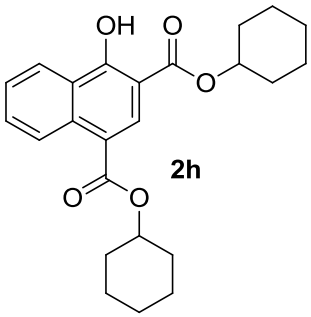
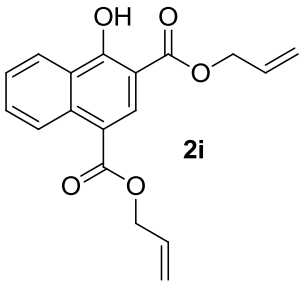
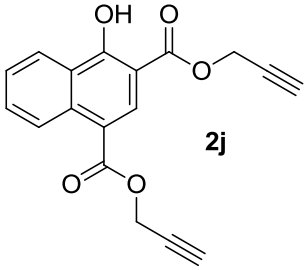
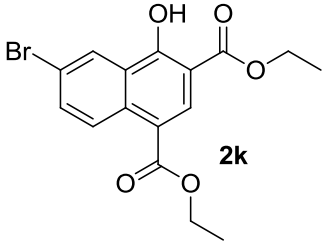
Having the optimum reaction conditions (10 mol% CuI, 2 equiv. of K_3PO_4, DMSO), the scope of the copper-catalyzed transformation of enol esters to α-naphthols was investigated (Table 4). When the (*E*)-2-(ethoxycarbonyl)vinyl 2-bromobenzoate was treated under similar reaction conditions, no trace of product was identified (from TLC) even on prolonged heating at 50 ºC. However, on raising the reaction temperature to 90 ºC, gave the target naphthol (**2a**) over a period of 12 h, albeit in lower yield (44%). Similarly, as expected, the less reactive (E)-2-(ethoxycarbonyl)vinyl 2-chlorobenzoate requires an even higher temperature (i.e., 150 ºC) to give naphthol **2a** in 30% yield over a period of 24 h. To our delight, reactions of other enol esters having variable chain lengths as well as substituents on the aromatic ring produced the substituted α-naphthols in moderate to good yield (55–82%).

Table 4: Cu-catalyzed synthesis of α-naphthols.

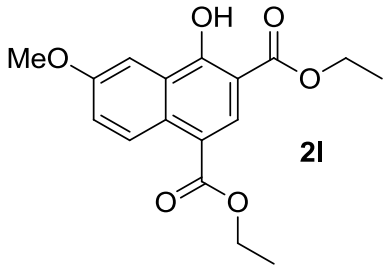
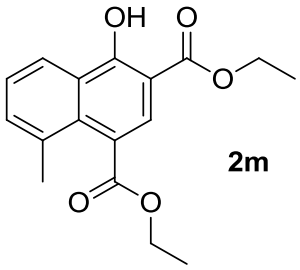
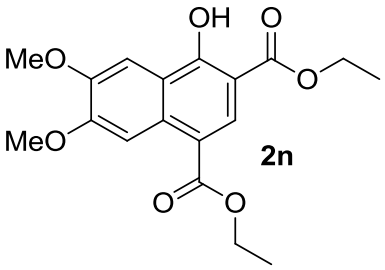


Entry	1	2	Yield (%)
1	**1a**	 **2a**	82%
2	**1b**	**2a**	44%
3	**1c**	**2a**	30%
4	**1d**	 **2b**	78%
5	**1e**	 **2c**	72%
6	**1f**	 **2d**	75%
7	**1g**	 **2e**	73%

Continued…

8	**1h**	 **2f**	74%
9	**1i**	 **2g**	77%
10	**1j**	 **2h**	84%
11	**1k**	 **2i**	67%
12	**1l**	 **2j**	55%
13	**1m**	 **2k**	68%

Continued…

14	**1n**	 **2l**	77%
15	**1o**	 **2m**	73%
16	**1p**	 **2n**	70%

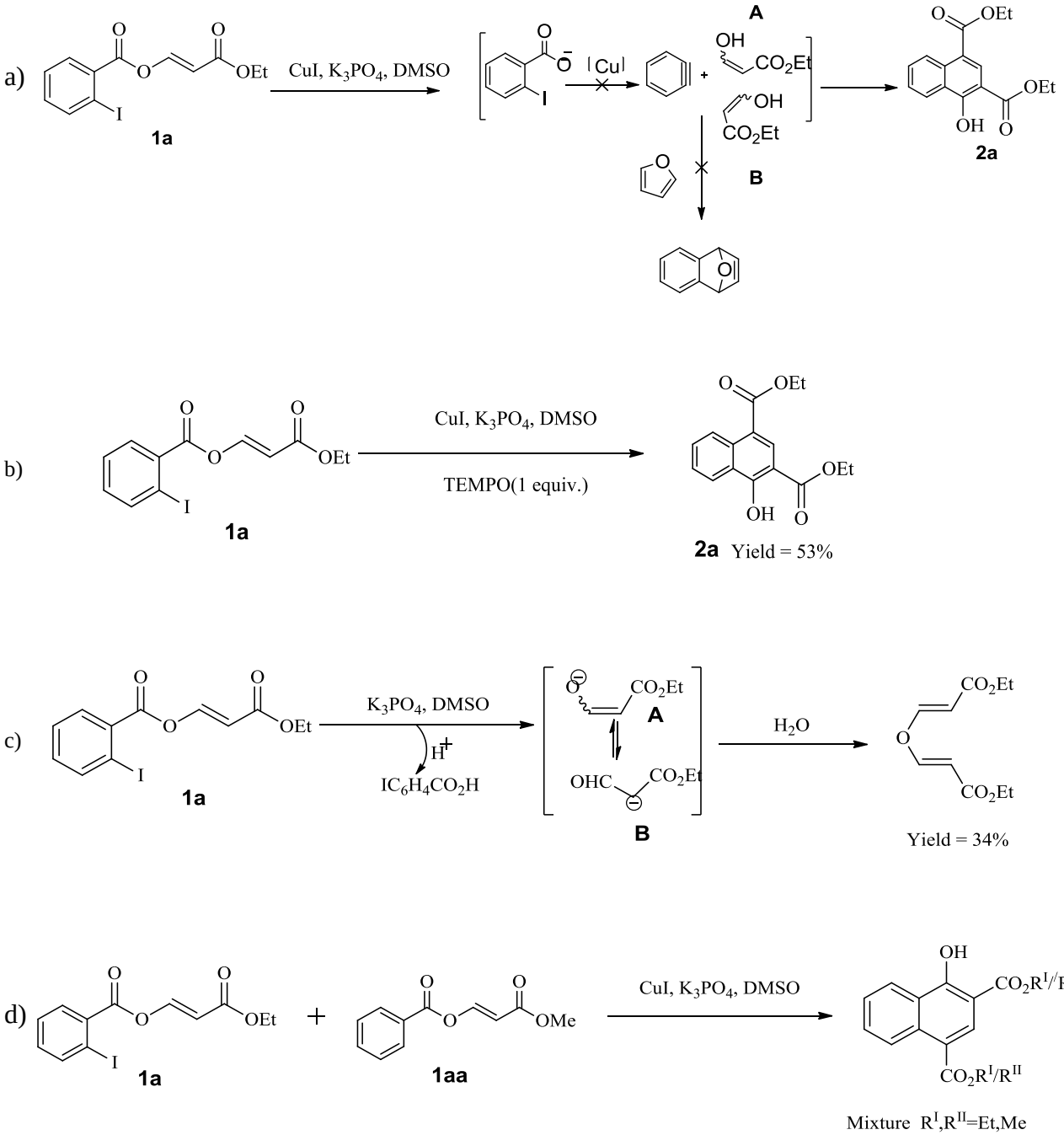
Reaction conditions: enol ester (1 equiv.), CuI (10 mol %), K_3PO_4 (2 equiv.), DMSO

Control experiments for insights into the mechanism

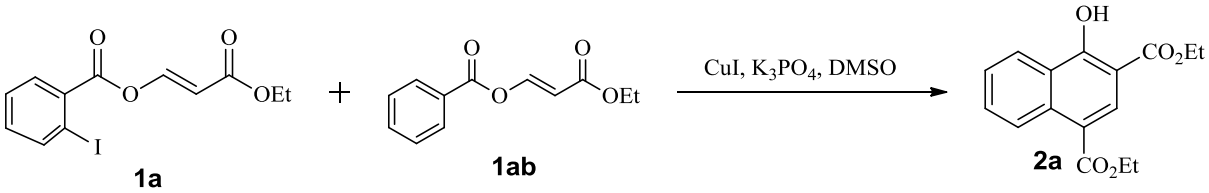
To gain insight into the copper-catalyzed cyclization of enol esters several controlled experiments, as presented in Scheme 3, were performed to elucidate the mechanism. Initially, the involvement of a [2+2+2] cycloaddition of benzyne with the generated enol (Scheme 3a) derived from the hydrolysis step was considered. However, a trapping experiment with furan was unsuccessful, implying that benzyne is not involved as an intermediate for this reaction. Furthermore, no radical intermediate was trapped by the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin1-yl oxyl), which ruled out the possibility of a radical pathway to achieve naphthols **2**(Scheme 3b). Next, when enol ester **1a** was treated under the optimum reaction conditions inthe absence of CuI, 3-(2-Ethoxy carbonyl-vinyloxy)-acrylic acid ethyl ester[20] (34%) as well as 2-iodobenzoic acid (from the acidification of the corresponding aqueous extract) were produced (Scheme 3c). This suggests that the first step of the reaction may be the hydrolysis step. Indeed, the presence of two ester groups in the naphthol product **2a**, indicates the involvement of two equivalents of enol esters **1a** to produce one equivalent of naphthol **2a.**

Notably, when an equimolar mixture of different enol esters (**1** and **1aa**) was treated under the optimum reaction conditions, an inseparable mixture of naphthols (from NMR spectra) was obtained (Scheme 3d). This will give information about the involvement of enolate intermediate in tandem annulation process. Moreover, the similar experimentation in the presence of 1 equiv. of enol ester **1a** reacted with enol ester **1ab**, resulted in naphthol **2a** in higher yield (68% with regard to 1 equiv. of enol ester 1); which further proves the involvement of enolate (e.g., A or B) intermediate in the tandem annulation process.

Scheme 3



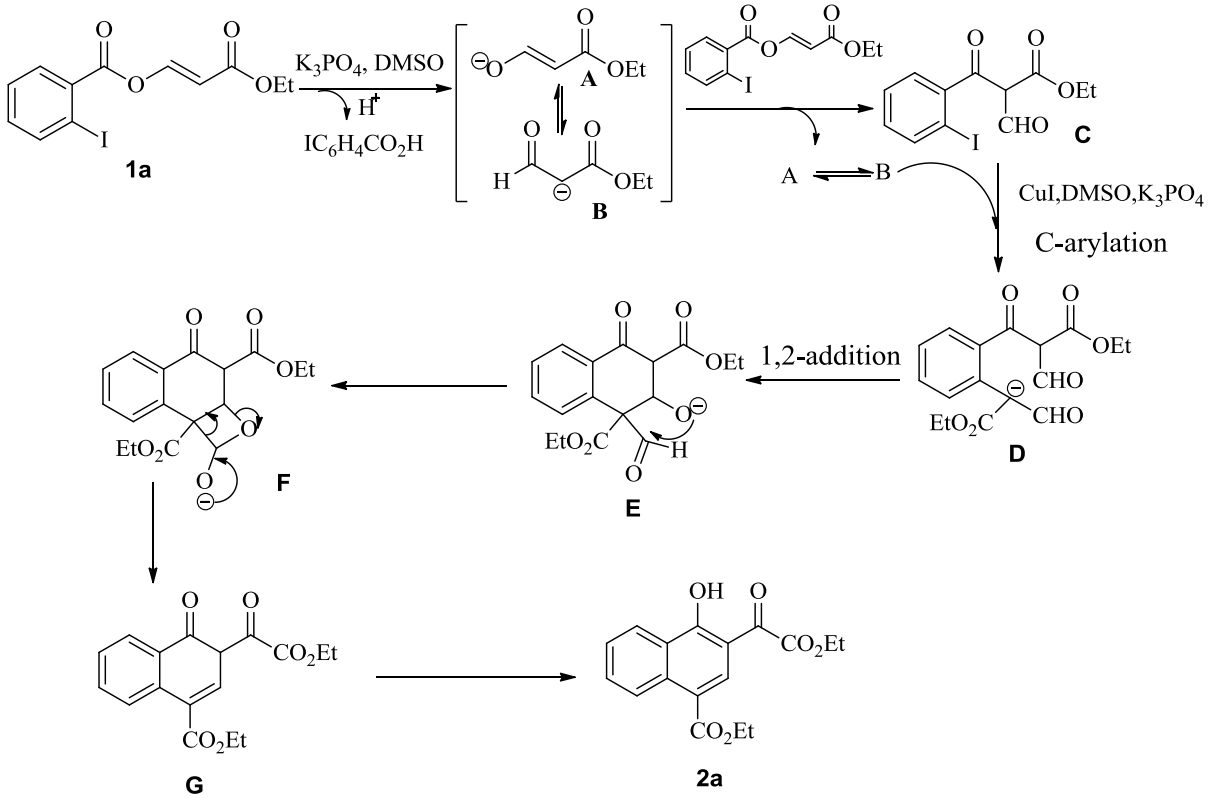
e)



Plausible mechanism

Based on the above observations, a plausible pathway for the regioselective synthesis of α-naphthol (**2a**) is outlined in Scheme. Initially, enol ester **1a** undergoes hydrolysis to enolate **A**, which on tautomerization leads to the intermediate B. Presumably, the intermediate **B**, thus formed reacts with another molecule of enol ester **1a** to produce **C**. In the presence of CuI and base in DMSO, intermolecular C-arylation[21] may take place to produce **D**. Next, the annulated intermediate E forms through the intramolecular 1,2-addition reaction of **D**. Subsequently, **E** undergoes rearrangement, followed by aromatization to afford the desired product **2a**.

Scheme 4



6.3 Conclusions

We have synthesized a number of enol esters by using the nucleophilic addition of benzoic acid derivatives to terminal alkynes in the presence of pyridine at room temperature for wirh good to excellent yield. The synthesized enol esters were employed for a Cu-catalyzed unprecedented synthesis of polysubstituted α-naphthols under mild reaction conditions. Further investigations to expand the application of this protocol to the synthesis of novel heterocyclic derivatives with detailed mechanistic studies are currently underway in our laboratory.

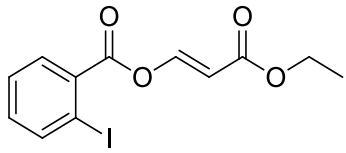
6.4 Experimental

General procedure for preparationofenolesters

A mixture of haloacid (1.0equiv), alkyl propiolate (1.1equiv) pyridine (2.0equiv) in15mL of toluene was stirred at room temperature. After12h the reaction mixture was diluted with ethylacetate (15mL) followed by 1N HCl solution.The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over the brine, anhydrous Na_2SO4 and then evaporated under reduced pressure. The crude residue was purified by column chromatography over the silicagel usinga mixture of petroleum ether and ethyl acetate as eluent to give the desired product.

Synthesis and analytical data for enol esters

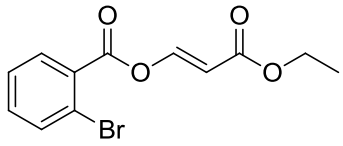
(*E*)-2-(ethoxycarbonyl)vinyl 2-iodobenzoate (1a)



Following method **A**, compound **1a** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and ethyl propiolate (216 mg, 2.21mmol) as a colourless solid (590 mg) in 85 % yield. MP 77-78 °C. IR (KBr): 3053, 2964, 2873, 1748, 1683, 1632, 1555, 1535, 1510, 1468, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 12.4 Hz), 8.09 (dd,1H, J_1 = 8.0 Hz, J_2 = 0.8 Hz), 7.97 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.52-7.46 (m, 1H), 7.28-7.23 (m, 1H), 5.92 (d, 1H, J = 12.4 Hz), 4.26 (q, 2H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 161.9, 149.5, 142.0, 133.9, 132.0, 131.9,

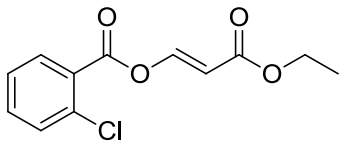
128.1, 107.0, 90.1, 60.6, 14.2. MS (ESI, +Ve) *m/z* (relative intensity) 369.02 ([M+Na],$^{+}$ 100%).

(*E*)-2-(ethoxycarbonyl)vinyl 2-bromobenzoate(1b)



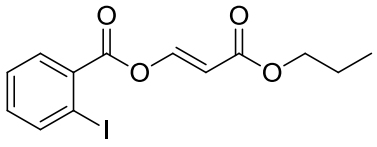
Following method **A**, compound **1b** was obtained from the reaction of 2-bromo benzoic acid (500 mg, 2.5 mmol) and ethyl propiolate (294 mg, 2.50mmol) as a colourless gummy liquid (598 mg) in 80 % yield. IR (KBr): 3088, 2982, 2919, 2835, 1744, 1650, 1591, 1234, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, 1H, *J* = 12.8 Hz), 7.93-7.89 (m, 1H) 7.70-7.67 (m, 1H) 7.42-7.37 (m, 2H), 5.87 (d, 1H, *J* = 12.4 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 161.4, 149.4, 134.9, 134.0, 132.2, 129.0, 127.4, 122.9, 106.9, 60.5, 14.2. MS (ESI, +Ve) *m/z* (relative intensity) 322.11 ([M+Na],+ 100%).

(*E*)-2-(ethoxycarbonyl)vinyl-2chlorobenzoate(1c)



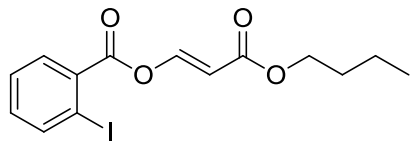
Following method **A**, compound **1c** was obtained from the reaction of 2-chloro benzoic acid (500 mg, 3.18mmol) and ethyl propiolate (343 mg, 3.50 mmol) as a colourless gummy liquid (671 mg) in 83 % yield. IR (KBr): 3098, 2980, 2916, 2845, 1748, 1717, 1656, 1591, 1234, 1014 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, *J* = 12.4 Hz), 8.01-7.96 (m, 1H), 7.55-7.53 (m, 2H), 7.43-7.37 (m, 1H), 5.90 (d, 1H, *J* = 12.4 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 1.33(t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.0, 149.4, 135.1, 134.0, 132.2, 131.6, 127.1, 126.8, 106.9, 60.6, 14.2. MS (ESI, + Ve) *m/z* (relative intensity) 277.00 ([M+Na],$^{+}$ 100%)

(*E*)-2-(propoxycarbonyl)vinyl 2-iodobenzoate (1d)



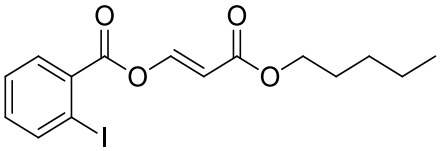
Following method **A**, compound **1d** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and propyl propiolate (248 mg, 2.21 mmol) as a colourless solid (566 mg) in 78 % yield. MP 74-75 °C. IR (KBr): 3090, 2966, 2885, 1755, 1718, 1653, 1581, 1464, 1430, 1389, 1285, 1232, 1062, 1032, 1011cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 12.8 Hz), 8.08 (dd, 1H, J_1 = 8 Hz, J_2 = 0.8 Hz), 7.97 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.50-7.45 (m, 1H), 7.28-7.22 (m, 1H), 5.92 (d, 1H, J = 12.4 Hz), 4.15 (t, 2H, J = 6.8 Hz), 1.76-1.67 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.8, 149.4, 142.1, 134.0, 131.9, 128.1, 107.0, 95.2, 66.2, 22.0, 10.4. MS (ESI, +Ve) *m/z* (relative intensity) 742.93 ([2M+Na], $^{+}$ 100%), 382.90 ([M+Na], $^{+}$ 80%).

(*E*)-2-(butoxycarbonyl)vinyl 2-iodobenzoate



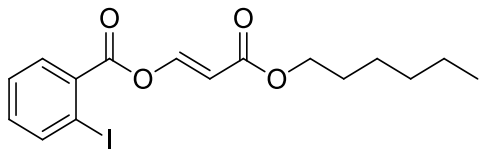
Following method **A**, compound **1e** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and butyl propiolate (279 mg, 2.211mmol) as a colorless solid (573 mg) in 76 % yield. MP 76-78 °C. IR (KBr): 3087, 2953, 2868, 1748, 1698, 1654, 1578, 1459, 1316, 1268, 1231, 1192, 1133, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, J = 12.8 Hz), 8.07 (t, 1H, J = 7.2 Hz), 7.97 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.50-7.45 (m, 1H), 7.28-7.22 (m, 1H), 5.91 (d, 1H, J = 12.4 Hz), 4.19 (t, 1H, J = 6.8 Hz), 1.72-1.63 (m, 2H), 1.46-1.39 (m, 2H), 0.96 (t, 3H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.03, 161.8, 149.4, 142.1, 134.0, 131.9, 128.1, 107.0, 95.2, 64.5, 30.6, 19.1, 13.7. MS (ESI, +Ve) *m/z* (relative intensity) 396.97 ([M+Na],$^{+}$ 100%).

(*E*)-2-((pentyloxy)carbonyl)vinyl 2-iodobenzoate (1f)



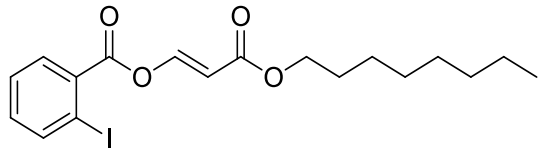
Following method A, compound **1f** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and ethyl propiolate (310 mg, 2.211mmol) as a colourless liquid (563 mg) in 72 % yield. IR (KBr): 3090, 2953, 2888, 2856, 1749, 1702, 1657, 1577, 1460, 1431, 1310, 1294, 1266, 1231, 1190, 1169, 1131, 1033, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, 1H, J = 12.4 Hz), 8.08 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.97 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.50-7.45 (m, 1H), 7.28-7.22 (m, 1H), 5.92 (d, 1H, J = 12.8 Hz), 4.19 (m, 2H), 1.72-1.65 (m, 2H), 1.40-1.33 (m, 4H), 0.96-0.90 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.8, 149.4, 142.1, 134.0, 131.9, 131.9, 128.1, 107.0, 95.2, 64.8, 28.3, 28.0, 22.3, 13.9. MS (ESI, + Ve) *m/z* (relative intensity) 411.00 ([M+Na],$^+$ 100%), 799.00 ([2M+Na],$^+$ 80%).

(*E*)-2-((hexyloxy)carbonyl)vinyl 2-iodobenzoate (1g)



Following method **A**, compound **1g** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and hexyl propiolate (340 mg, 2.21mmol) as a colourless liquid (656mg) in 81 % yield. IR (KBr): 3251, 3090, 2954, 2928, 2857, 2116, 1755, 1718, 1655, 1581, 1561, 1465, 1430, 1378, 1285, 1231, 1169, 1106, 1032, 1011 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, J = 12.4 Hz), 8.09 (d, 1H, J = 14.4 Hz), 7.98 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.28-7.23 (m, 1H), 5.93 (d, 1H, J = 12.4 Hz), 4.20 (t, 2H, J = 6.8 Hz), 1.74-1.65 (m, 2H), 1.44-1.32 (m, 6H), 0.92 (t, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.9, 149.4, 142.1, 134.0, 131.9, 128.1, 107.0, 95.1, 66.8, 31.4, 28.6, 25.6, 22.5, 14.0. MS (ESI, + Ve) *m/z* (relative intensity) 425.09 ([M+Na],$^+$ 100%)

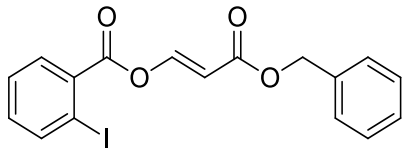
(*E*)-2-((octyloxy)carbonyl)vinyl 2-iodobenzoate (1h)



Following method **A**, compound **1h** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and octyl propiolate (372 mg, 2.21mmol) as a colourless liquid (590 mg) in 85 % yield. IR (KBr): 3089, 2941, 2925, 2850, 1749, 1703, 1657, 1577, 1464,

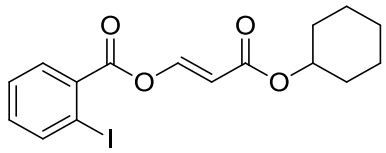
1432, 1314, 1267, 1230, 1193, 1132, 1107, 1031, 1010cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, 1H, J = 12.4 Hz), 8.04 (dd, 1H, J_1 = 8 Hz, J_2 = 1.2 Hz), 7.93 (dd, 1H, J_1 = 8 Hz, J_2 = 1.6 Hz), 7.47-7.41 (m, 1H), 7.24-7.18 (m, 1H), 5.88 (d, 1H, J = 12.4 Hz), 4.15 (t, 2H, J = 6.8 Hz), 1.69-1.61 (m, 2H), 1.36-1.24 (m, 10H), 0.85 (t, 3H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 161.8, 149.4, 142.1, 134.0, 132.0, 131.8, 128.1, 107.0, 95.2, 64.8, 31.8, 29.2, 29.2, 28.6, 25.9, 22.6, 14.1. MS (ESI, + Ve) *m/z* (relative intensity) 453.09 ([M+Na], $^{+}$ 100%).

(*E*)-2-((benzyloxy)carbonyl)vinyl 2-iodobenzoate (1i)



Following method **A**, compound **1i** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and benzyl propiolate (354 mg, 2.21mmol) as a colourless liquid (658 mg) in 80 % yield. IR (KBr): 3086, 3053, 2952, 1752, 1718, 1654, 1580, 1455, 1272, 1230, 1090, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, 1H, J = 12.4 Hz), 8.08 (dd, 1H, J_1 = 8 Hz, J_2 = 0.8 Hz), 7.97 (dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 7.47 (t, 1H, J = 0.8 Hz), 7.43-7.37 (m, 5H), 7.28-7.24 (m, 1H), 5.98 (d, 1H, J = 12.4 Hz), 5.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 161.8, 149.9, 142.1, 135.7, 134.1, 132.0, 131.7, 128.6, 128.3, 128.3, 128.2, 106.7, 95.3, 66.4. MS (ESI, +Ve) *m/z* (relative intensity) 838.84 ([2M+Na],$^{+}$ 100%), 430.90 ([M+Na],$^{+}$ 50%).

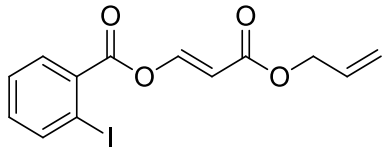
(*E*)-2-((cyclohexyloxy)carbonyl)vinyl 2-iodobenzoate (1j)



Following method **A**, compound **1j** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and cyclohexyl propiolate (336 mg, 2.21mmol) as yellow oil (588 mg) in 73 % yield. IR (KBr): 3282, 2913, 2845, 1751, 1718, 1683, 1642, 1577, 1457, 1429, 1370, 1221 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, 1H, J = 12.4 Hz), 8.05 (dd, 1H, J = 8 Hz), 7.94 (dd, 1H, J = 8 Hz), 7.49-7.43 (m, 1H), 7.26-7.20 (m, 1H), 5.89 (d, 1H, J = 12.4 Hz), 4.90-4.82 (m, 1H), 1.92-1.86 (m, 2H), 1.77-1.72 (m, 2H), 1.57-1.23 (m,

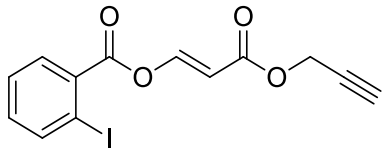
6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 161.9, 149.2, 142.0, 134.0, 131.9, 131.9, 128.1, 107.5, 95.2, 72.9, 31.6, 25.3, 23.7. MS (ESI, + Ve) *m/z* (relative intensity) 423.01 ([M+Na],$^+$ 100%).

(*E*)-2-((allyloxy)carbonyl)vinyl 2-iodobenzoate (1k)



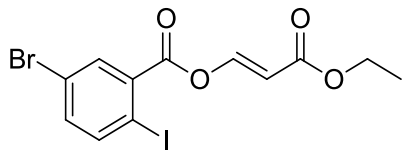
Following method **A**, compound **1k** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and allyl propiolate (243 mg, 2.21mmol) as a colourless liquid (512 mg) in 71 % yield. IR (KBr): 3086, 2916, 2840, 1754, 1718, 1654, 1580, 1429, 1273, 1230, 1105, 1006 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, 1H, J = 12.4 Hz), 8.08 (d, 1H, J = 8.0 Hz), 7.97 (dd, 1H, J_1 = 8 Hz, J_2 = 1.6 Hz), 7.49 (dd, 1H, J_1 = 11.2 Hz, J_2 = 0.8 Hz), 7.28-7.22 (m, 1H), 6.03-5.92 (m, 2H), 5.40-5.26 (m, 2H), 4.70 (d, 2H, J = 5.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 161.8, 149.8, 142.1, 134.0, 132.0, 131.9, 128.1, 118.5, 106.6, 95.2, 65.2. MS (ESI, + Ve) *m/z* (relative intensity) 380.95 ([M+Na],$^+$ 100%), 738.8 ([2M+Na],$^+$ 40%)

(*E*)-2-((prop-2-ynyloxy)carbonyl)vinyl 2-iodobenzoate (1l)



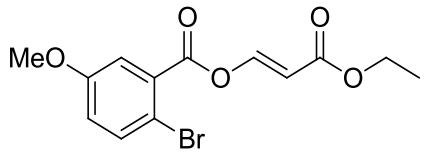
Following method **A**, compound **1l** was obtained from the reaction of 2-iodo benzoic acid (500 mg, 2.01mmol) and prop-2-ynyl propiolate (239 mg, 2.21mmol) as a colourless liquid (545 mg) in 76 % yield. IR (KBr): 3088, 2925, 2851, 2135, 1753, 1718, 1658, 1573, 1435, 1374, 1272, 1245, 1131, 1103, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ8.59 (d, 1H, J =12.4 Hz), 8.09 (t, 1H, J = 7.6 Hz), 7.98 (dd, 1H, J_1 = 8 Hz, J_2 = 1.6 Hz), 7.52-7.45 (m, 1H), 7.28-7.23 (m, 1H), 5.95 (d, 1H, J = 12.4), 4.80 (d, 2H, J = 2.4 Hz), 2.53 (t, 1H, J = 2.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 161.7, 150.5, 142.1, 134.1, 132.0, 131.7, 128.1, 105.9, 95.3, 77.4, 75.1, 52.1. MS (ESI, + Ve) *m/z* (relative intensity) 356.11 ([M+1],$^+$ 100%)

(*E*)-2-(ethoxycarbonyl)vinyl 5-bromo-2-iodobenzoate (1m)



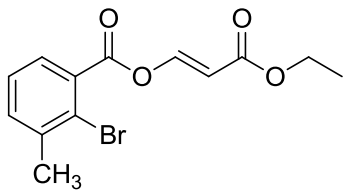
Following method **A**, compound **1m** was obtained from the reaction of 5-bromo-2-iodo benzoic acid (500 mg, 1.528 mmol) and ethyl propiolate (165 mg, 1.68mmol) as yellow oil (512 mg) in 79 % yield. IR (KBr): 3411, 3095, 3002, 2864, 2851, 1714, 1652, 1596, 1568, 1475, 1435, 1409, 1315, 1018 cm.$^{-1}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, 1H, *J* = 12.8 Hz), 8.05 (d, 1H, *J* = 2.4 Hz), 7.91 (d, 1H, *J* = 8.8 Hz), 7.36 (dd, 1H, J_1 = 8.8, J_2 = 2.4 Hz), 5.94 (d, 1H, *J* = 12.8 Hz), 4.26 (q, 2H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 160.7, 149.1, 143.3, 136.9, 134.6, 133.6, 122.4, 107.6, 93.1, 60.7, 14.2. MS (ESI, + Ve) *m/z* (relative intensity) 446.90 ([M+Na],$^{+}$ 100%).

(*E*)-2-(ethoxycarbonyl)vinyl 2-bromo-5-methoxybenzoate (1n)



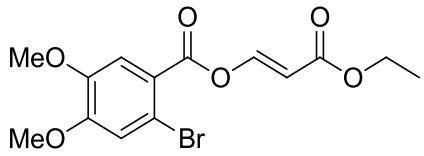
Following method **A**, compound **1n** was obtained from the reaction of 2-bromo-5-methoxybenzoic acid (500 mg, 2.164mmol) and ethyl propiolate (212 mg, 2.38mmol) as a colourless solid (512 mg) 72 % yield. MP 64-66 °C. IR (KBr): 3090, 2978, 2929, 2845, 1758, 1717, 1655, 1594, 1567, 1474, 1402, 1367, 1315, 1242, 1281, 1211, 1176 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, 1H, *J* = 12.4), 7.59 (d, 1H, *J* = 8.8 Hz), 7.43 (d, 1H, *J* = 3.2 Hz), 6.98 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.8 Hz), 5.91 (d, 1H, *J* = 12.8 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 3.84 (S, 3H), 1.35-1.30 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 161.5, 158.6, 149.4, 135.6, 129.7, 120.2, 117.2, 113.1, 107.0, 60.6, 55.7, 14.2. MS (ESI, +Ve) *m/z* (relative intensity) 351.00 ([M+Na],$^{+}$ 100%).

(*E*)-2-(ethoxycarbonyl)vinyl 2-bromo-3-methylbenzoate (1o)



Following method **A**, compound **1o** was obtained from the reaction of 2-bromo-3-methylbenzoic acid (500 mg, 2.32mmol) and ethyl propiolate (250 mg, 2.55mmol) as a colourless liquid (508 mg) in 70 % yield. IR (KBr): 3090, 2980, 2929, 1758, 1718, 1655, 1575, 1447, 1407, 1367, 1311, 1280, 1264, 1240, 1174, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.51 (d, 1H, J = 12.4 Hz), 7.64 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz), 7.44 (t, 1H, J = 0.8 Hz), 7.30 (dd, 1H, J_1 = 12.6 Hz, J_2 = 7.6 Hz), 5.87 (d, 1H, J = 12.4 Hz), 4.24 (q, 2H, J = 7.2Hz), 2.48 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 162.5, 149.5, 140.4, 134.6, 130.7, 129.0, 126.9, 124.3, 106.9, 60.6, 23.9, 14.2. MS (ESI, + Ve) *m/z* (relative intensity) 334.99 ($[M+Na]^+$, 100%).

(*E*)-2-(ethoxycarbonyl)vinyl 2-bromo-4,5-dimethoxybenzoate (1p)



Following the general method **A**, compound **1p** was obtained from the reaction of 2-bromo-4,5-dimethoxybenzoic acid (500 mg, 1.915mmol) and ethyl propiolate (206 mg, 2.106 mmol) as a colourless solid (557 mg) in 81 % yield. MP 58-60 °C. IR (KBr): 3092, 2980, 2913, 2840, 1748, 1713, 1650, 1594, 1511, 1265, 1205, 1174, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, 1H, J = 12.4 Hz), 7.48 (s, 1H), 7.14 (s, 1H), 5.89 (d, 1H, J = 12.4 Hz), 4.24 (q, 2H, J = 7.2 Hz), 3.94 (s, 3H), 3.92 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 160.9, 153.2, 149.6, 147.9, 119.9, 117.4, 116.0, 114.3, 106.5, 60.5, 56.4, 56.2, 14.2. MS (ESI, +Ve) m/z (relative intensity) 380.86 ($[M+Na]$,$^+$ 100%).

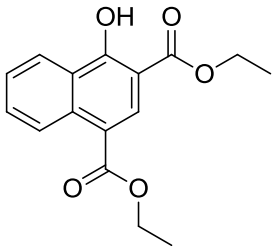
Method B: General procedure for synthesis of naphthols

A mixture of enol ester (100 mg), CuI (10 mol %), K_3PO_4 (2 equiv.) in DMSO (3 mL) was stirred at 50 °C, unless otherwise noted. Progress of the reaction was monitored by TLC. After the time mentioned in Table 1, the reaction mixture was quenched with 1N HCl solution and then diluted with ethyl acetate. Two layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over brine and anhydrous Na_2SO_4 and then evaporated under reduced pressure. The crude residue was purified by using column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate as eluent to give the desired α-naphthols. Yields of

naphthols were calculated by considering the reaction of 2 molar equiv of enol ester to 1 molar equiv of naphthol.

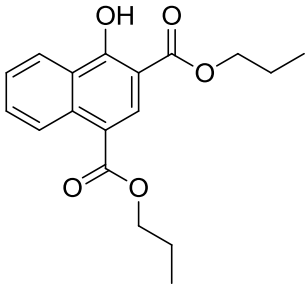
Synthesis and analytical data of α-naphthols

Diethyl-4-hydroxynaphthalene-1, 3-dicarboxylate (2a)



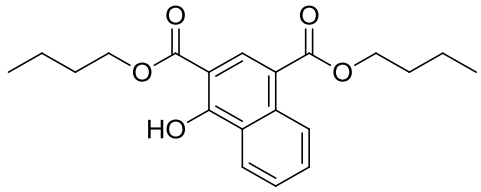
Following method **B**, compound **2a** was obtained from **1a** (100 mg, 0.29 mmol) as a colourless solid (34 mg) in 82 % yield. MP 97-98 °C. IR (KBr): 3467, 3081, 2922, 2851, 1725, 1664, 1625, 1577, 1504, 1409, 1370, 1337, 1240, 1155, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.52 (s, 1H), 9.00 (d, 1H, *J* = 8.8 Hz), 8.62 (s, 1H), 8.49 (d, 1H, *J* = 7.6 Hz), 7.78-7.71(m, 1H), 7.63-7.56 (m, 1H), 4.55-4.43 (m, 4H), 1.53-1.46 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.8, 164.2, 135.0, 130.9, 130.4, 126.0, 125.9, 125.0, 124.1, 118.0, 104.8, 61.8, 60.9, 14.4, 14.2. HRMS (TOF ESI +ve) m/z *[*M + H]$^{+}$ calcd. For $C_{16}H_{17}O_5$, 289.3088; found, 289.3073.

Dipropyl-4-hydroxynaphthalene-1, 3-dicarboxylate (2b)



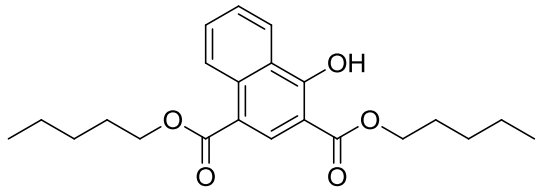
Following method **B**, compound **2b** was obtained from **1d** (100 mg, 0.277 mmol) as a colourless solid (34 mg) in 78 % yield. MP 83-85°C. IR (KBr): 3439, 3092, 2957, 2922, 2857, 1711, 1665, 1613, 1577, 1479, 1415, 1252, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.49 (s, 1H), 9.02 (d, 1H, *J* = 8.4 Hz), 8.66 (s, 1H), 8.50 (t, 1H, *J* = 7.6 Hz), 7.78-7.72 (m, 1H), 7.63-7.57 (m, 1H), 4.44 - 4.35 (m, 4H), 1.93-1.84 (m, 4H), 1.10 (t, 6H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 166.8, 164.1, 135.1, 130.9, 130.5, 126.0, 125.9, 125.0, 124.1, 118.1, 104.8, 67.2, 66.4, 22.1, 22.0, 10.6, 10.4. HRMS (TOF ESI +ve) *m/z* [M + Na]$^{+}$ calcd. for $C_{18}H_{20}O_5Na$, 339.3420; found, 339.3436.

Dibutyl-4-hydroxynaphthalene-1, 3-dicarboxylate (2c)



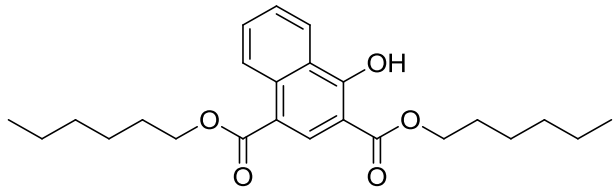
Following method **B**, compound **2c** was obtained from **1e** (100 mg, 0.267 mmol) as a colourless solid (33 mg) in 72 % yield. MP 69-70 °C. IR (KBr): 3450, 3226, 2957, 2913, 2847, 1714, 1664, 1610, 1482, 1441, 1274, 1252, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ12.48 (s, 1H), 9.02 (d, 1H, *J* = 8.4 Hz), 8.64 (s, 1H), 8.48 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.8 Hz), 7.77-7.70 (m, 1H), 7.65-7.55 (m, 1H), 4.47-4.39 (m, 4H), 1.88-1.80 (m, 4H), 1.60-1.50 (m, 4H), 1.04 (t, 6H, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.8, 164.1, 135.1, 130.9, 130.5, 126.0, 125.9, 125.0, 124.1, 118.0, 104.8, 65.6, 64.7, 30.8, 30.5, 19.4, 19.2, 13.8, 13.7. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{25}O_5$, 345.1702; found, 345.1795.

Dipentyl-4-hydroxynaphthalene-1, 3-dicarboxylate (2d)



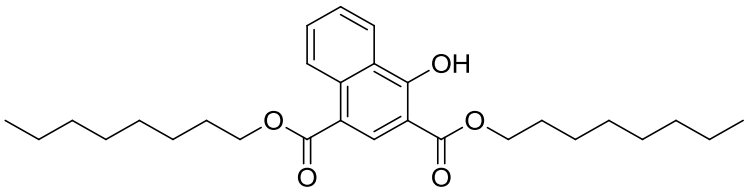
Following method **B**, compound **2d** was obtained from **1f** (100 mg, 0.257 mmol) as a colourless solid (36 mg) in 75 % yield. MP 65-66 °C. IR (KBr): 3428, 3058, 2956, 2868, 1790, 1739, 1664, 1460, 1412, 1342, 1251, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.48 (d, 1H, *J* = 3.6 Hz), 9.04-8.99 (m, 1H), 8.62 (d, 1H, *J* = 3.2 Hz), 8.50-8.45 (m, 1H), 7.76-7.70 (m, 1H), 7.59-7.54 (m, 1H), 4.45-4.36 (m, 4H), 1.85 (t, 4H, *J* = 6.4 Hz), 1.55-1.43 (m, 8H), 1.0-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.7, 164.1, 135.1, 130.9, 130.5, 126.0, 125.9, 125.0, 124.0, 117.9, 104.8, 65.9, 65.0, 28.4, 28.3, 28.2, 28.1, 22.3, 22.3, 14.0, 13.9. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{22}H_{29}O_5$, 373.4627; found, 373.4616.

Dihexy-l 4-hydroxynaphthalene-1, 3-dicarboxylate (2e)



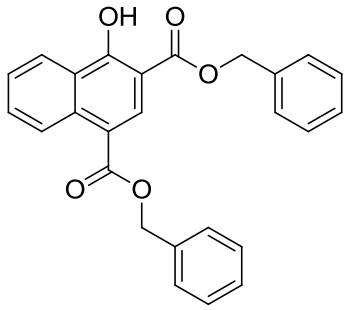
Following method **B**, compound **2e** was obtained from **1g** (100 mg, 0.248 mmol) as a colourless liquid (36 mg) in 73 % yield. IR (KBr): 3462, 3070, 2929, 2856, 1728, 1710, 1663, 1622, 1574, 1448, 1409, 1341, 1252, 1159, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ12.50 (s, 1H), 9.02 (d, 1H, *J* = 8.4 Hz), 8.64 (s, 1H), 8.49 (d, 1H, *J* = 8.8 Hz), 7.77-7.70 (m, 1H), 7.62 - 7.55 (m, 1H), 4.46-4.37 (m, 4H), 1.88-1.83 (m, 4H), 1.53-1.49 (m, 4H), 1.40-1.36 (m, 8H), 0.98-0.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 166.8, 164.1, 135.1, 130.9, 130.5, 126.0, 125.9, 125.0, 124.1, 118.0, 104.8, 65.9, 65.0, 31.4, 31.4, 28.7, 28.5, 25.8, 25.6, 22.6, 22.5, 14.0. HRMS (TOF ESI +ve) *m/z* $[M + Na]^+$ calcd. for $C_{24}H_{32}O_5Na$, 423.2177; found, 423.2200.

Dioctyl 4-hydroxynaphthalene-1,3-dicarboxylate (2f):



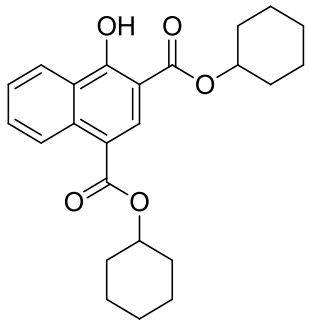
Following method **B**, compound **2f** was obtained from **1h** (100 mg, 0.232 mmol) as a colourless liquid (38 mg) in 74 % yield. IR (KBr): 3456, 3064, 2953, 2924, 2853, 1711, 1664, 1628, 1576, 1507, 1464, 1412, 1341, 1251, 1186, 1157, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.49 (s, 1H), 9.02 (d, 1H, *J* = 8.8 Hz), 8.63 (s, 1H), 8.49 (d, 1H, *J* = 8.4 Hz), 7.75-7.71 (m, 1H), 7.61-7.55 (m, 1H), 4.46-4.37 (m, 4H), 1.88-1.82 (m, 4H), 1.52-1.45 (m, 4H), 1.43-1.30 (m, 16H), 0.93-0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.8, 164.1, 135.1, 130.9, 130.5, 126.0, 125.9, 125.0, 124.1, 118.0, 104.8, 65.9, 65.0, 31.8, 31.8, 29.2, 29.2, 28.8, 28.5, 26.1, 25.9, 22.6, 14.1. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{28}H_{41}O_5$, 457.2954; found, 457.3001.

Dibenzyl 4-hydroxynaphthalene-1,3-dicarboxylate (2g)



The reaction of (*E*)-2-((benzyloxy)carbonyl)vinyl 2-iodobenzoate (**1i**) (100 mg, 0.245 mmol) with K_3PO_4 (114 mg, 0.49 mmol) and CuI (10 mol%) at room temperature for 24 h gave **2g** as a colourless solid (39 mg) in 77 % yield. MP 117-119 °C. IR (KBr): 3445, 3064, 3036, 2924, 1708, 1662, 1575, 1504, 1451, 1414, 1343, 1273, 1256, 1235, 1187, 1162 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.42 (s, 1H), 9.04 (d, 1H, *J* = 8.4 Hz), 8.75 (s, 1H), 8.50 (t, 1H, *J* = 7.6 Hz), 7.77-7.74 (m, 1H), 7.63-7.59 (m, 1H), 7.51-7.48 (m, 1H), 7.45-7.37 (m, 10H), 5.48 (s, 2H), 5.48 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 166.3, 164.5, 136.2, 135.2, 135.1, 131.2, 130.8, 128.7, 128.6, 128.2, 128.1, 128.0, 126.2, 125.9, 125.0, 124.1, 117.6, 104.6, 67.3, 66.5. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{26}H_{21}O_5$, 413.4419; found, 413.4428.

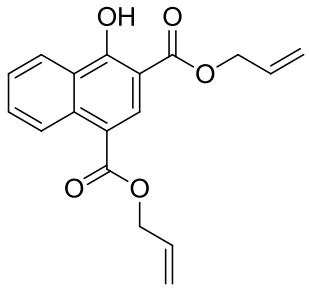
Dicyclohexyl 4-hydroxynaphthalene-1,3-dicarboxylate (2h)



Following method **B**, compound **2h** was obtained from **1j** (100 mg, 0.25 mmol) as a colourless solid (42 mg) in 84 % yield. MP 102-104 °C. IR (KBr): 3439, 3053, 2932, 2856, 1708, 1661, 1627, 1574, 1507, 1449, 1406, 1356, 1250, 1155, 1160, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ12.56 (s, 1H), 9.01 (d, 1H, *J* = 8.4 Hz), 8.67 (s, 1H), 8.48 (dd, 1H, J_1 = 0.8 Hz, J_2 = 8.4 Hz), 7.77-7.70 (m, 1H), 7.60-7.54 (m, 1H), 5.22-5.11 (m, 2H), 2.06-1.98 (m, 4H), 1.88-1.82 (m, 4H), 1.78-1.67 (m, 4H), 1.62-1.55 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 166.3, 164.0, 135.0, 130.7, 130.6, 125.9, 125.9, 125.0, 124.0, 118.4,

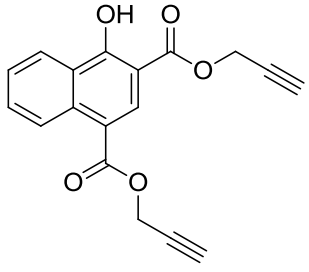
105.2, 74.1, 72.8, 31.6, 31.4, 25.5, 25.3, 23.5, 23.3. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{24}H_{29}O_5$, 397.4841; found, 397.4828.

Diallyl 4-hydroxynaphthalene-1,3-dicarboxylate (2i)



The reaction of (*E*)-2-((allyloxy)carbonyl)vinyl 2-iodobenzoate **1k** (100 mg, 0.279 mmol) with K_3PO_4 (118 mg, 0.558 mmol) and CuI (10 mol%) in DMSO (3 mL) at room temperature for 24 h gave **2i** as a colourless liquid (29 mg) in 67 % yield. IR (KBr): 3462, 3092, 2942, 1745, 1716, 1666, 1622, 1577, 1402, 1334, 1253, 1234, 1184, 1152 $cm.^{-1}$ ^1H NMR (400 MHz, $CDCl_3$): δ 12.42 (s, 1H), 9.03 (d, 1H, *J* = 8.8 Hz), 8.71 (s, 1H), 8.50 (d, 1H, *J* = 7.6 Hz), 7.79-7.73 (m, 1H), 7.63-7.60 (m, 1H), 6.16-6.07(m, 2H), 5.53-5.45 (m, 2H), 5.41-5.32 (m, 2H), 4.97-4.90(m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ170.1, 166.2, 164.4, 135.1, 132.4, 131.4, 131.1, 130.6, 126.1, 125.9, 125.0, 124.1, 119.2, 118.2, 117.6, 104.6, 66.2, 65.5. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{18}H_{27}O_5$, 313.3245; found, 313.3233.

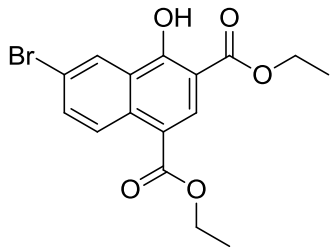
Diprop-2-ynyl 4-hydroxynaphthalene-1,3-dicarboxylate (2j)



The reaction of **1l** (100 mg, 0.28 mmol) with K_3PO_4 (120 mg, 0.56 mmol) and CuI (10 mol%) in DMSO (3 mL) at room temperature for 24 h gave **2j** (55 % yield) as a inseparable mixture with **1l** (from ^1H NMR). IR (KBr): 3289, 3088, 2925, 2857, 2128, 1755, 1723, 1656, 1579, 1506, 1431, 1370, 1271, 1230, 1131, 1102, 1062, 1035, 1007 cm^{-1}; ^1H

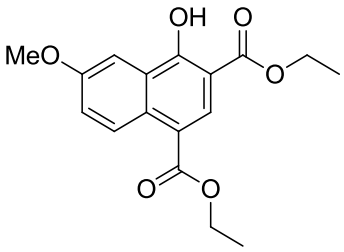
NMR (400 MHz, $CDCl_3$): δ 12.23 (s, 1H), 9.06 (d, 1H, *J* = 8.8 Hz), 8.73 (s, 1H), 8.51 (d, 1H, *J* = 9.2 Hz), 7.99-7.77 (m, 1H), 7.65-7.60 (m, 1H), 5.96 (d, 2H, *J* = 12.8 Hz), 5.06 (d, 2H, *J* = 2.8 Hz), 2.62 (t, 1H, *J* = 2.4 Hz), 2.57 (t, 1H, *J* = 2.4 Hz)

Diethyl 6-bromo-4-hydroxynaphthalene-1,3-dicarboxylate (2k)



Following method **B**, compound **2k** was obtained from the reaction of **1m** (100 mg, 0.235 mmol) as a colourless solid (27 mg) in 68 % yield. MP 86-88 °C. IR (KBr): 3731, 3417, 2957, 2921, 2845, 1713, 1665, 1569, 1488, 1406, 1380, 1332, 1238, 1152, 1105, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.50 (s 1H), 8.93 (d, 1H, *J* = 9.2 Hz), 8.62 (s, 1H), 7.80 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 4.56-4.43 (m, 4H), 1.53-1.44 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ170.3, 166.3, 163.0, 134.0, 133.6, 130.7, 127.9, 126.4, 126.3, 120.5, 118.0, 105.7, 62.1, 61.0, 14.4, 14.2. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{16}H_{16}BrO_5$, 367.0181; found, 367.0198.

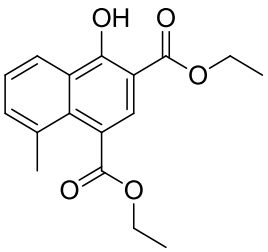
Diethyl 4-hydroxy-6-methoxynaphthalene-1,3-dicarboxylate (2l)



The reaction of **1n** (100 mg, 0.303 mmol) with K_3PO_4 (129 mg, 0.606 mmol) and CuI (10 mol %) in DMSO (3 mL) at 90 °C for 12 h gave **2l** as a colourless solid (34 mg) in 77 % yield. MP 106-108 °C. IR (KBr): 3731, 3092, 2977, 2907, 1728, 1708, 1661, 1606, 1509, 1407, 1251, 1182, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.47 (s, 1H), 8.93 (d, 1H, *J* = 9.2 Hz), 8.50 (s, 1H), 7.76 (d, 1H, *J* = 2.8 Hz), 7.38 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.4 Hz), 4.55- 4.43 (m, 4H), 3.98 (s, 3H), 1.53-1.45 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 166.9, 162.9, 157.6, 130.3, 128.0, 127.6, 126.4, 123.0, 118.1, 105.2, 102.3, 61.8,

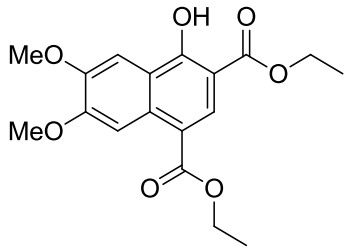
60.8, 55.4, 14.4, 14.2. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{17}H_{19}O_6$, 319.1981; found, 319.1992.

Diethyl 4-hydroxy-8-methylnaphthalene-1,3-dicarboxylate (2m)



The reaction of **1o** (100 mg, 0.319 mmol) with K_3PO_4 (135 mg, 0.638 mmol) and CuI (10 mol %) in DMSO (3 mL) at 90 °C for 12 h gave **2m** as a colourless liquid (32 mg) in 73 % yield. IR (KBr): 3434, 3058, 2978, 2924, 1724, 1663, 1622, 1507, 1453, 1408, 1335, 1243, 1183, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ12.27 (s, 1H), 8.40 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz), 7.54-7.48 (m, 2H), 4.52-4.41 (m, 4H), 2.60 (s, 3H), 1.50-1.41 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 17.04, 162.7, 134.0, 133.3, 132.7, 126.4, 126.1, 125.9, 122.5, 122.4, 104.1, 61.7, 61.6, 22.0, 14.2, 14.1. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{17}H_{19}O_5$, 303.1232; found, 303.1226.

Diethyl 4-hydroxy-6,7-dimethoxynaphthalene-1,3-dicarboxylate (2n)



The reaction of **1p** (100 mg, 0.278 mmol) with K_3PO_4 (106 mg, 0.556 mmol) and CuI (10 mol%) in DMSO (3 mL) at 90 °C for 12 h gave **2n** as a colourless solid (34 mg) in 70% yield. MP 125-127 °C. IR (KBr): 3452, 3109, 2935, 2885, 1700, 1656, 1610, 1586, 1510, 1475, 1431, 1405, 1377, 1341, 1252, 1226, 1162, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ12.42 (s, 1H), 8.61 (s, 1H), 8.59 (s, 1H), 7.73 (s, 1H), 4.54-4.42 (m, 4H), 4.09 (s, 3H), 4.06 (s, 3H), 1.52-1.46 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 167.0, 162.6, 153.1, 149.0, 132.1, 129.5, 120.1, 116.0, 105.6, 104.0, 102.6, 61.7, 60.7, 55.9, 55.9, 14.4, 14.2. HRMS (TOF ESI +ve) *m/z* $[M + H]^+$ calcd. for $C_{18}H_{21}O_7$, 349.1262; found, 349.1287.

X-Ray crystallography of 2a

Diffraction data was collected on a Bruker SMART APEX CCD-based X-Ray diffractometer, equipped with a MoK/α probe on a wavelength of 0.71073 Å. The data integration and reduction were processed with SAINT software.[22] An empirical absorption correction was applied to the collected reflections with SADABS.[23] The structures were solved by direct methods using SHELXTL[24] and were refined on F^2 by the full-matrix least-squares technique using the SHELXL-97[25] program package. Graphics are generated using ORTEP. All non- hydrogen atoms were refined anisotropically and hydrogen atoms were placed in ideal positions and refined as rigid atoms with individual isotropic thermal displacement parameters.

Crystallographic data (CCDC 936097) for ***2a*** $C_{16}H_{16}O_5$; M_r = 288.29; Colorless needle shaped crystals were grown from a mixture of ethyl acetate and dichloromethane. Dimensions of the specimen used for X-ray experiments 0.26 × 0.22 × 0.12 mm^3. Space group Monoclinic $P_{21/n}$. Lattice constants (Å) a = 11.132(4), b = 6.731(2), c = 18.771(7), β = 94.065(7)°. Cell volume V = 1403.0(8) ($Å^3$), z =4, X-ray density ρ_x = 1.365 mg m^{-3}, $2\theta_{max}$ = 52.72, number of independent reflections = 1949, reflections collected = 2851, linear absorption coeff. μ = 0.102 mm^{-1}, R_{int} = 0.0396. After convergence of refinements R_1 = 0.0584/0.0864, R_W, = 0.1504/0.1995, GoF = 1.033.

6.5 References

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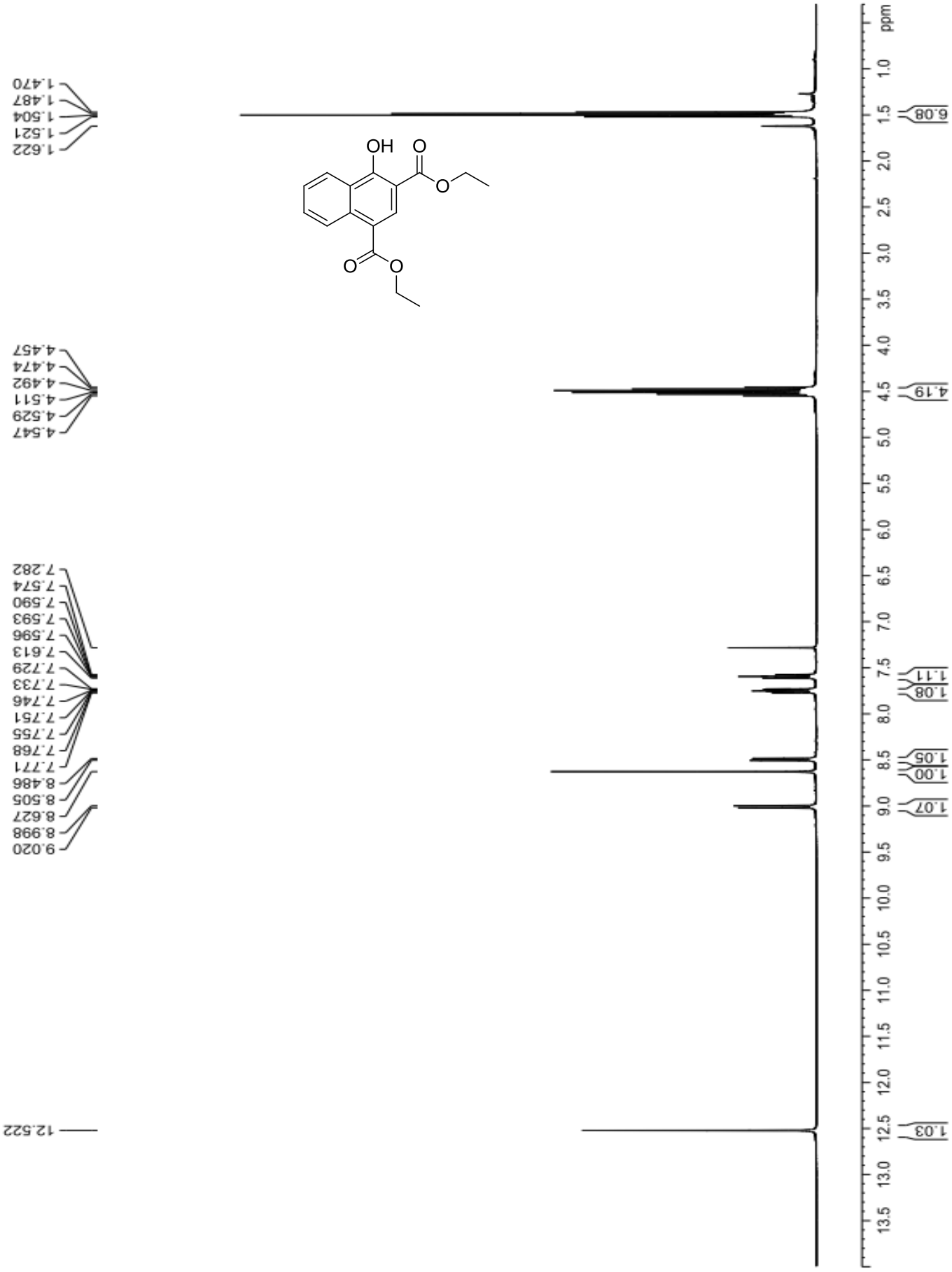
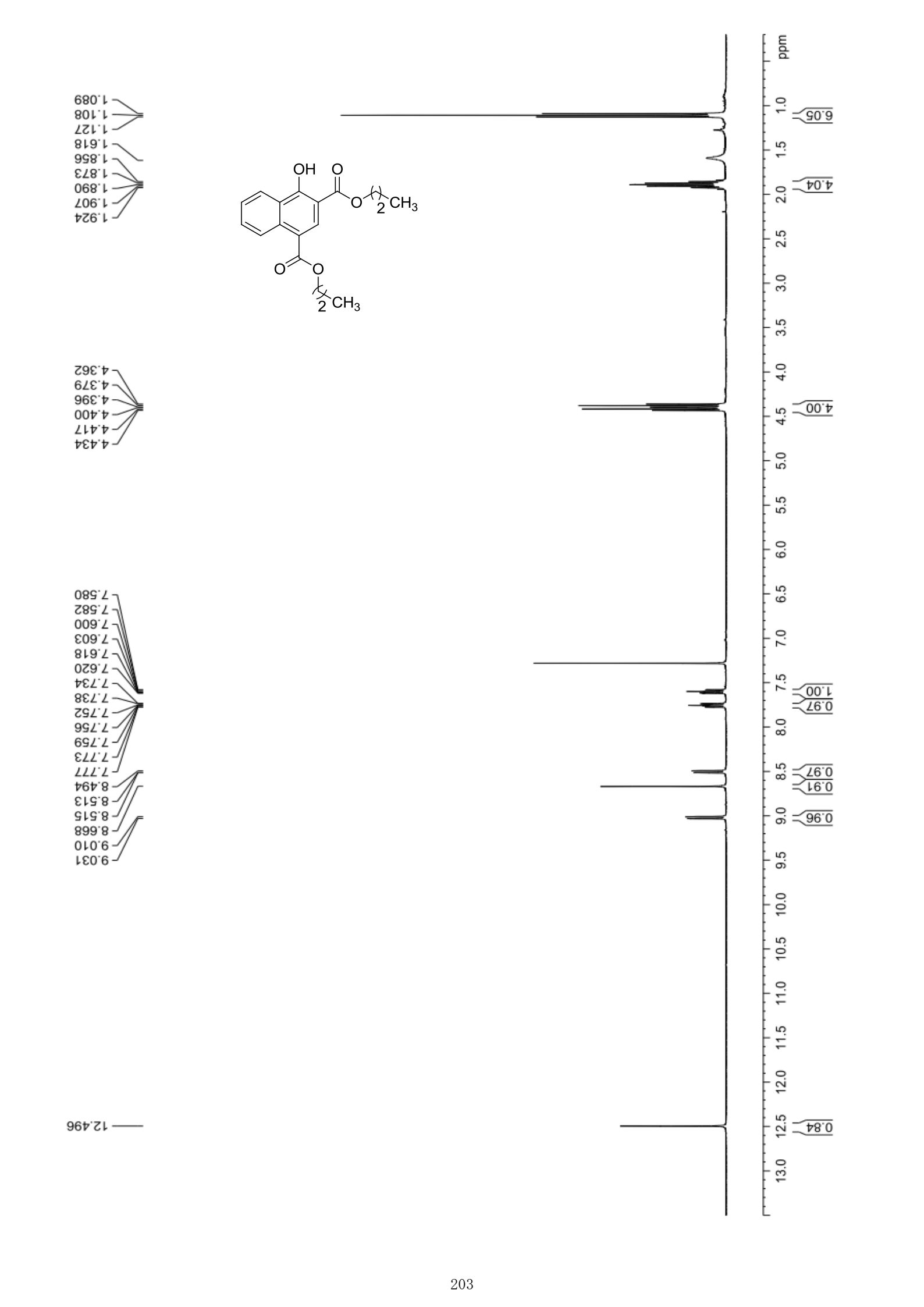
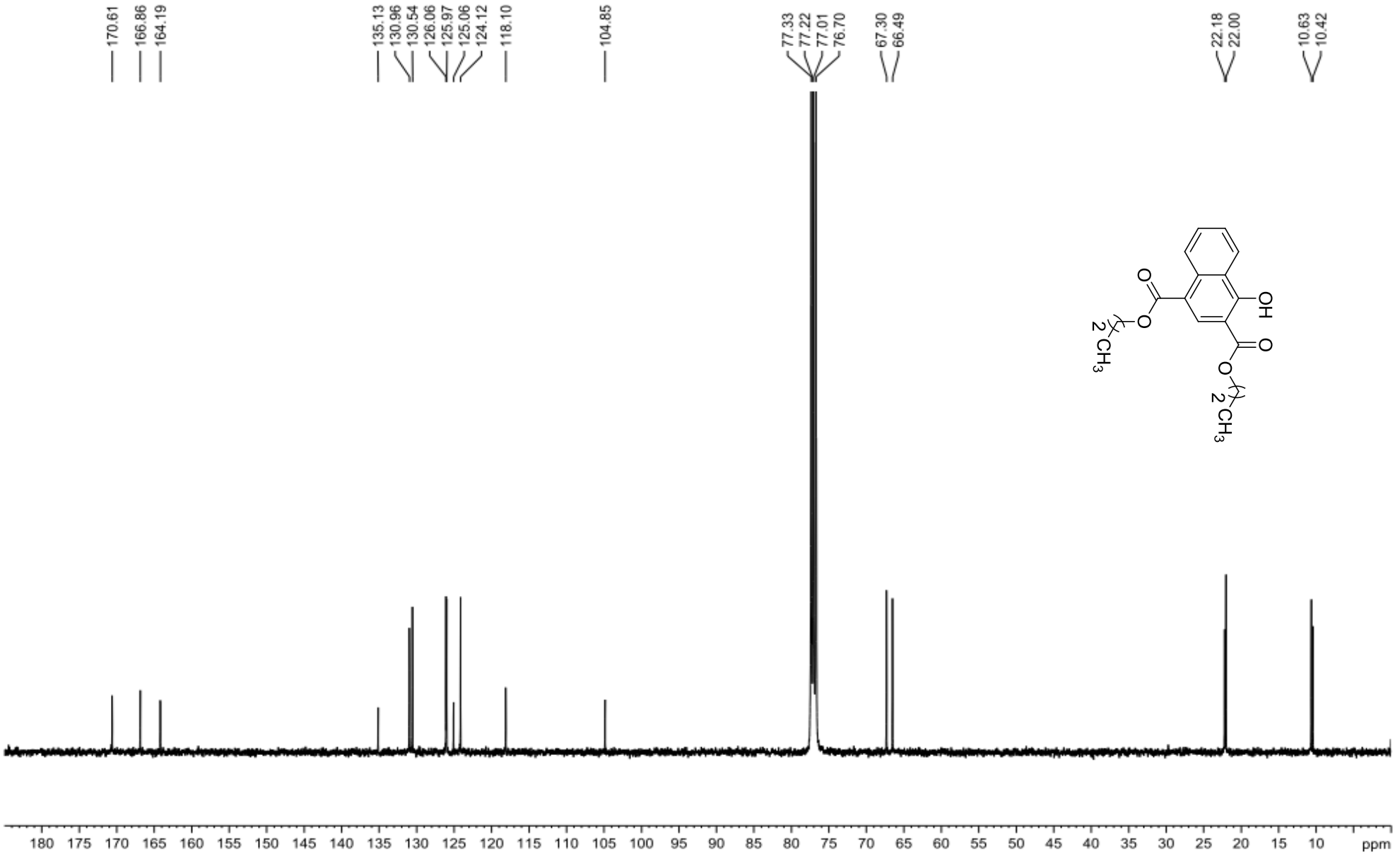
6.6 Selected NMR Spectra

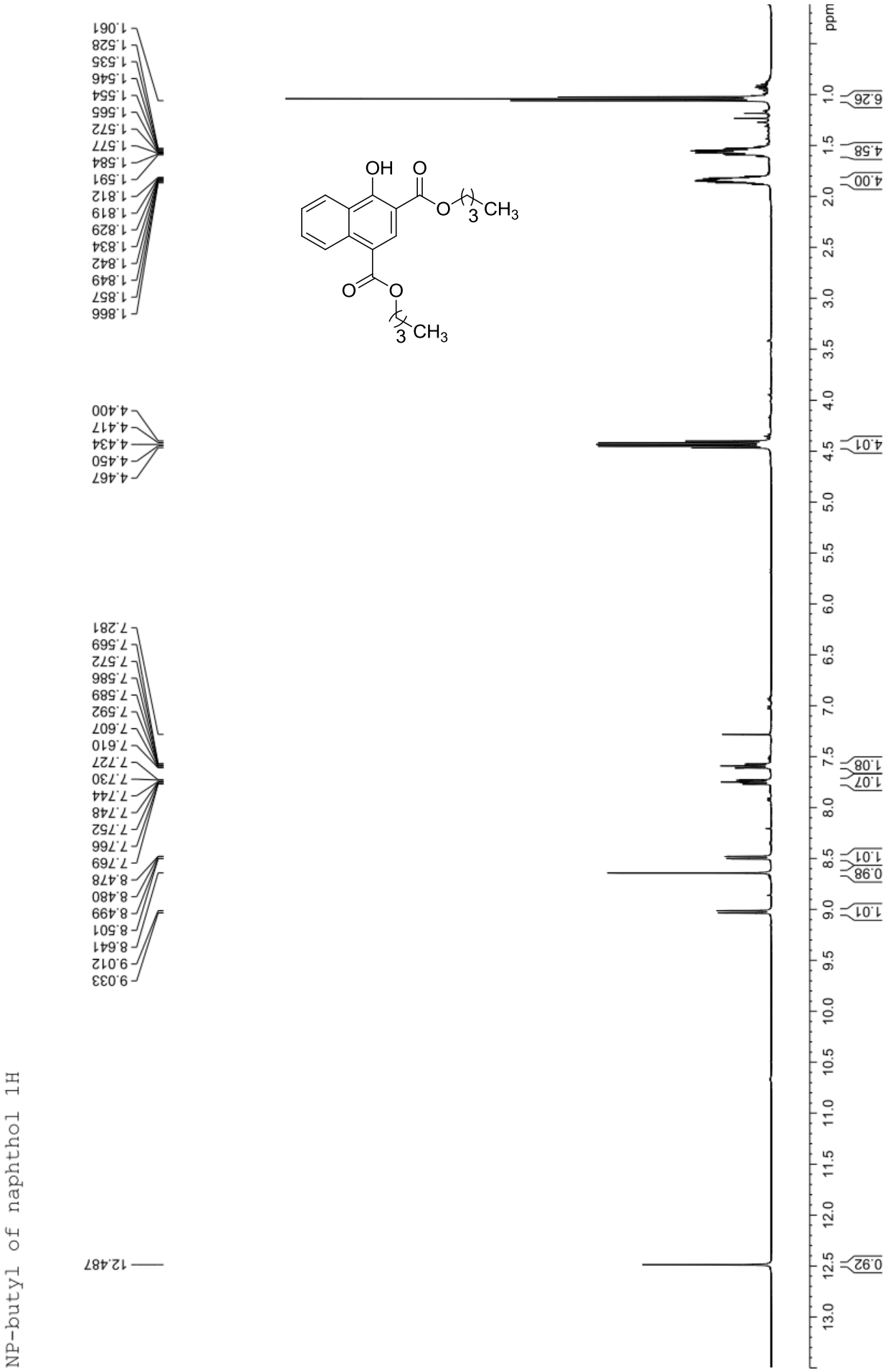



naphthol+ethyl 13C
14.27
14.45
60.91
61.89
76.70
77.02
77.34
104.81
118.09
124.12
125.04
125.96
126.05
130.47
130.94
135.08
164.20
166.82
170.59
OH
O
O
O
O
ppm

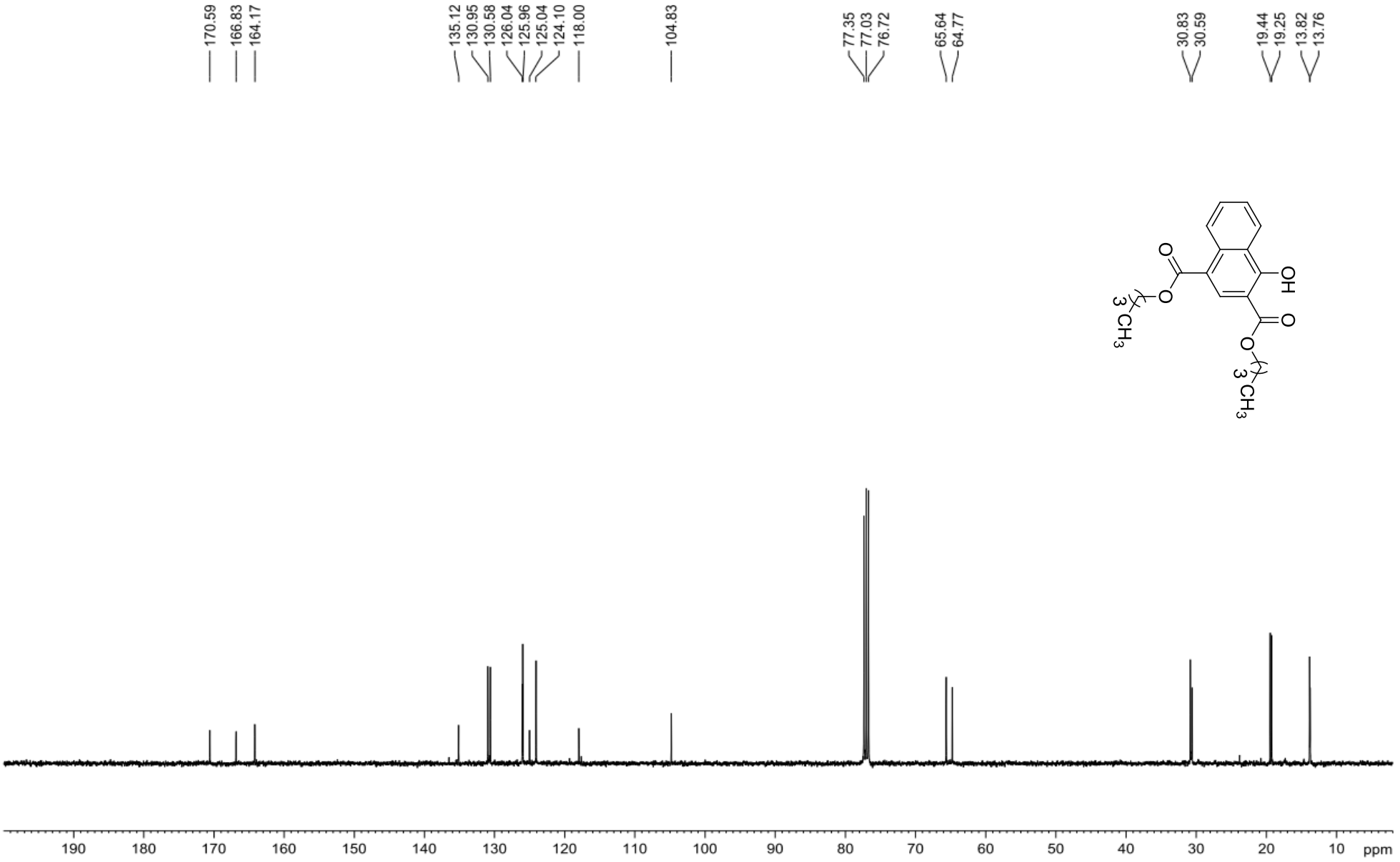

OH
O
O
2
CH3
O
O
2
CH3
1.089
1.108
1.127
1.618
1.856
1.873
1.890
1.907
1.924
4.362
4.379
4.396
4.400
4.417
4.434
7.580
7.582
7.600
7.603
7.618
7.620
7.734
7.738
7.752
7.756
7.759
7.773
7.777
8.494
8.513
8.515
8.668
9.010
9.031
12.496
6.05
4.04
4.00
1.00
0.97
0.97
0.91
0.96
0.84
ppm

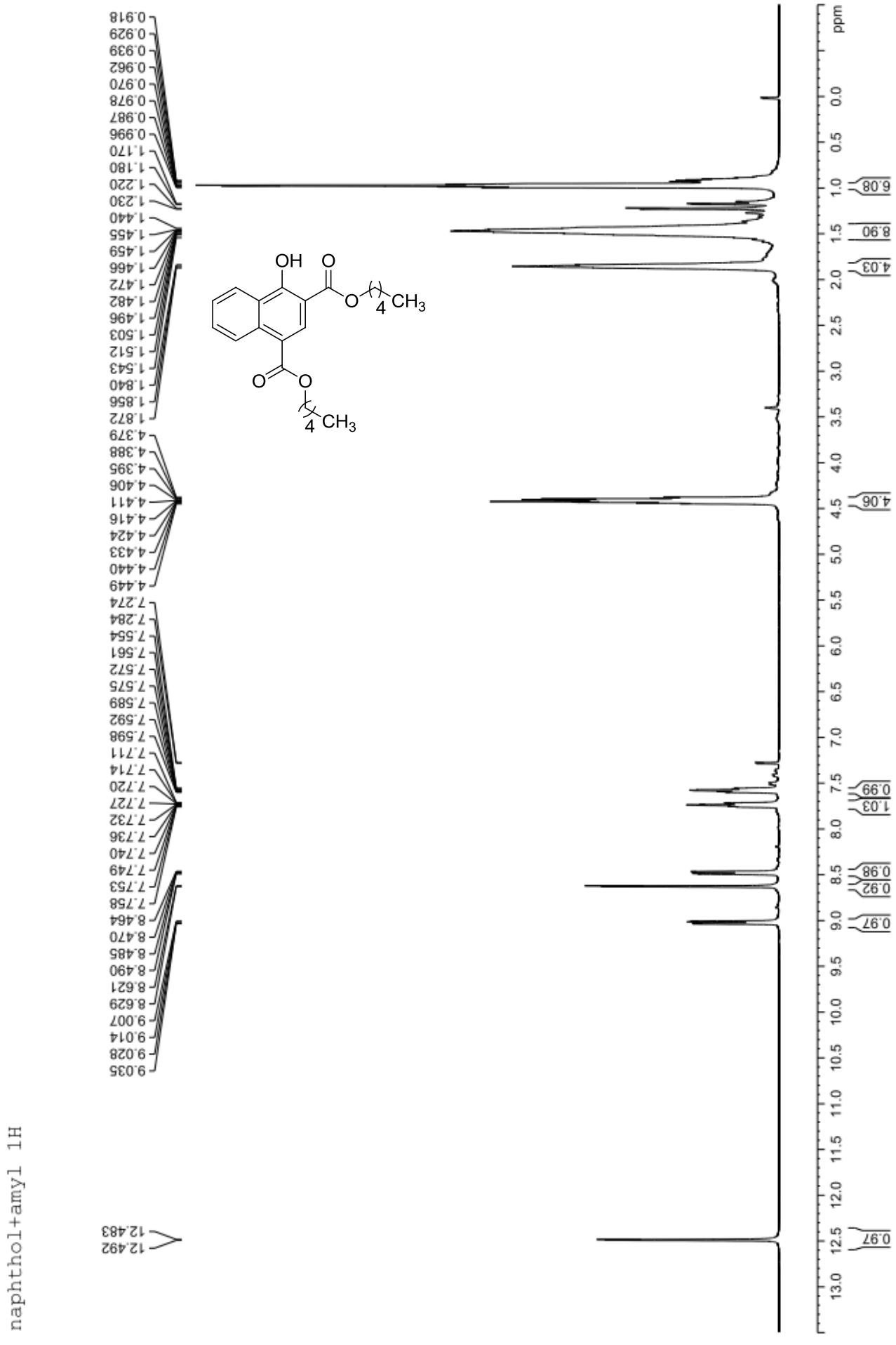
naphthol+propyl 13C

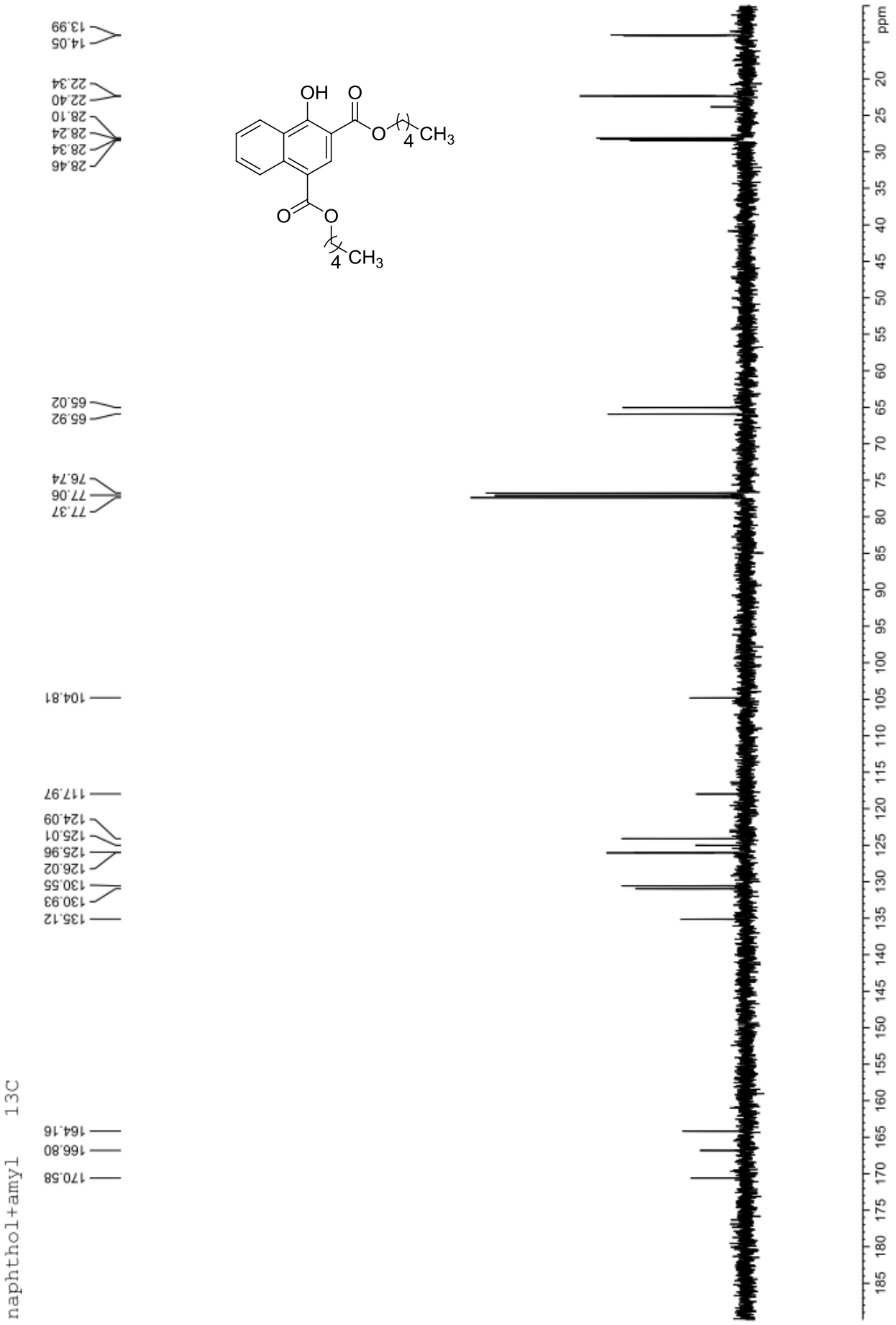



NP-butyl of naphthol 1H
OH
O
O
O
3
CH3
O
O
3
CH3
ppm
6.26
4.58
4.00
4.01
1.08
1.07
1.01
0.98
1.01
0.92
1.061
1.528
1.535
1.546
1.554
1.565
1.572
1.577
1.584
1.591
1.812
1.819
1.829
1.834
1.842
1.849
1.857
1.866
4.400
4.417
4.434
4.450
4.467
7.281
7.569
7.572
7.586
7.589
7.592
7.607
7.610
7.727
7.730
7.744
7.748
7.752
7.766
7.769
8.478
8.480
8.499
8.501
8.641
9.012
9.033
12.487

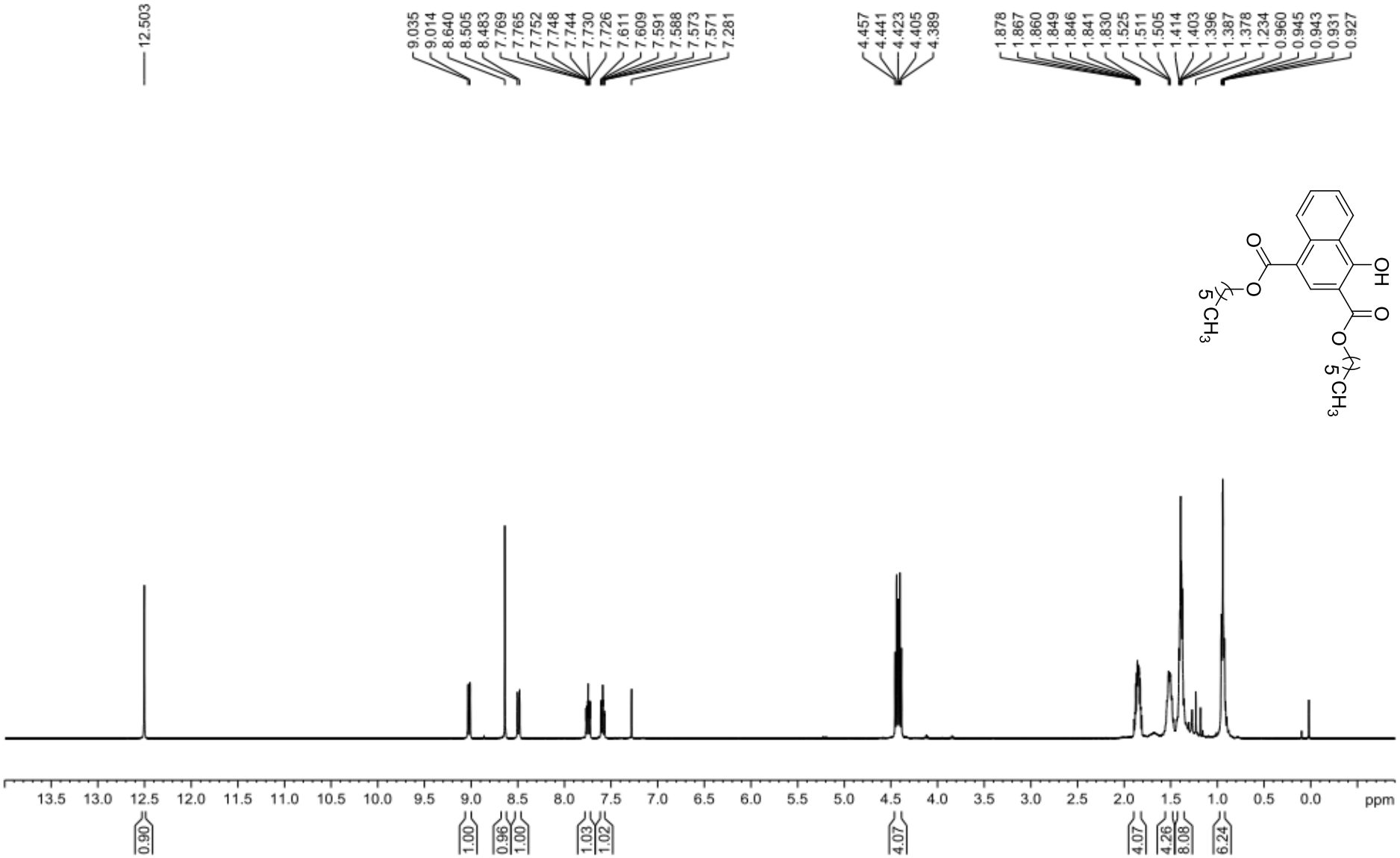
NP-butyl+naphthol 13C

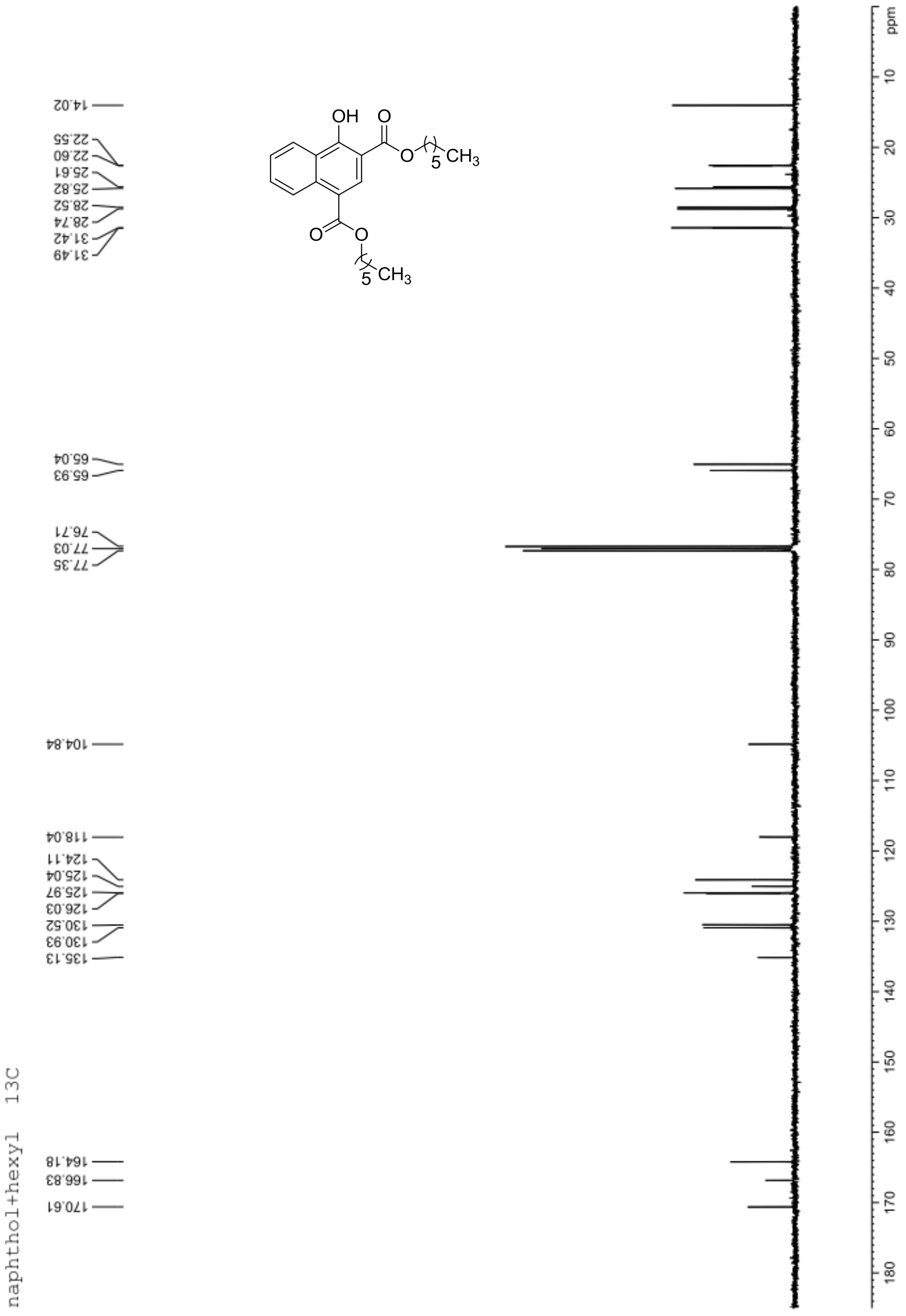


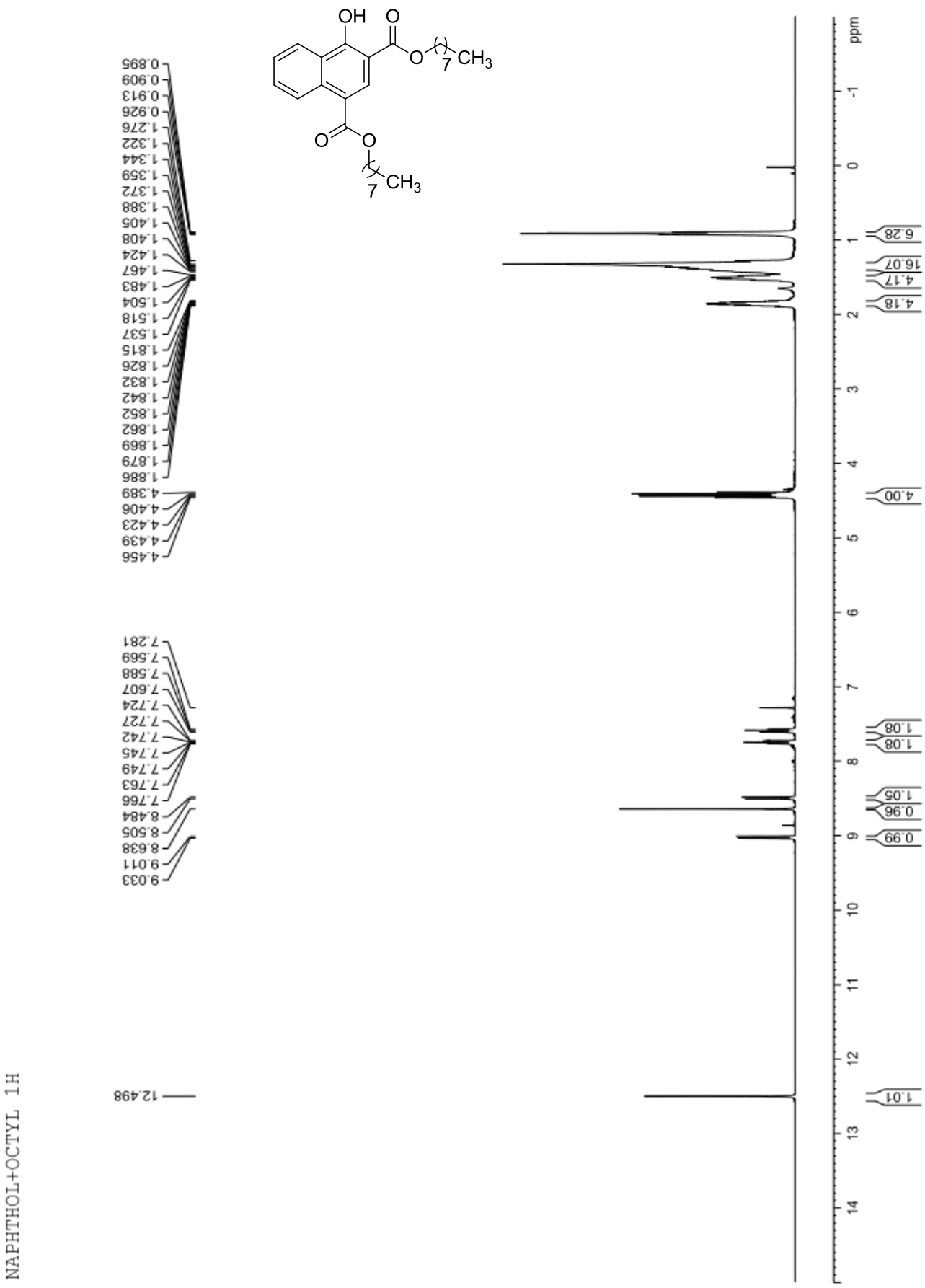

naphthol+amyl 1H
OH
O
O
4
CH3
O
O
4
CH3
ppm

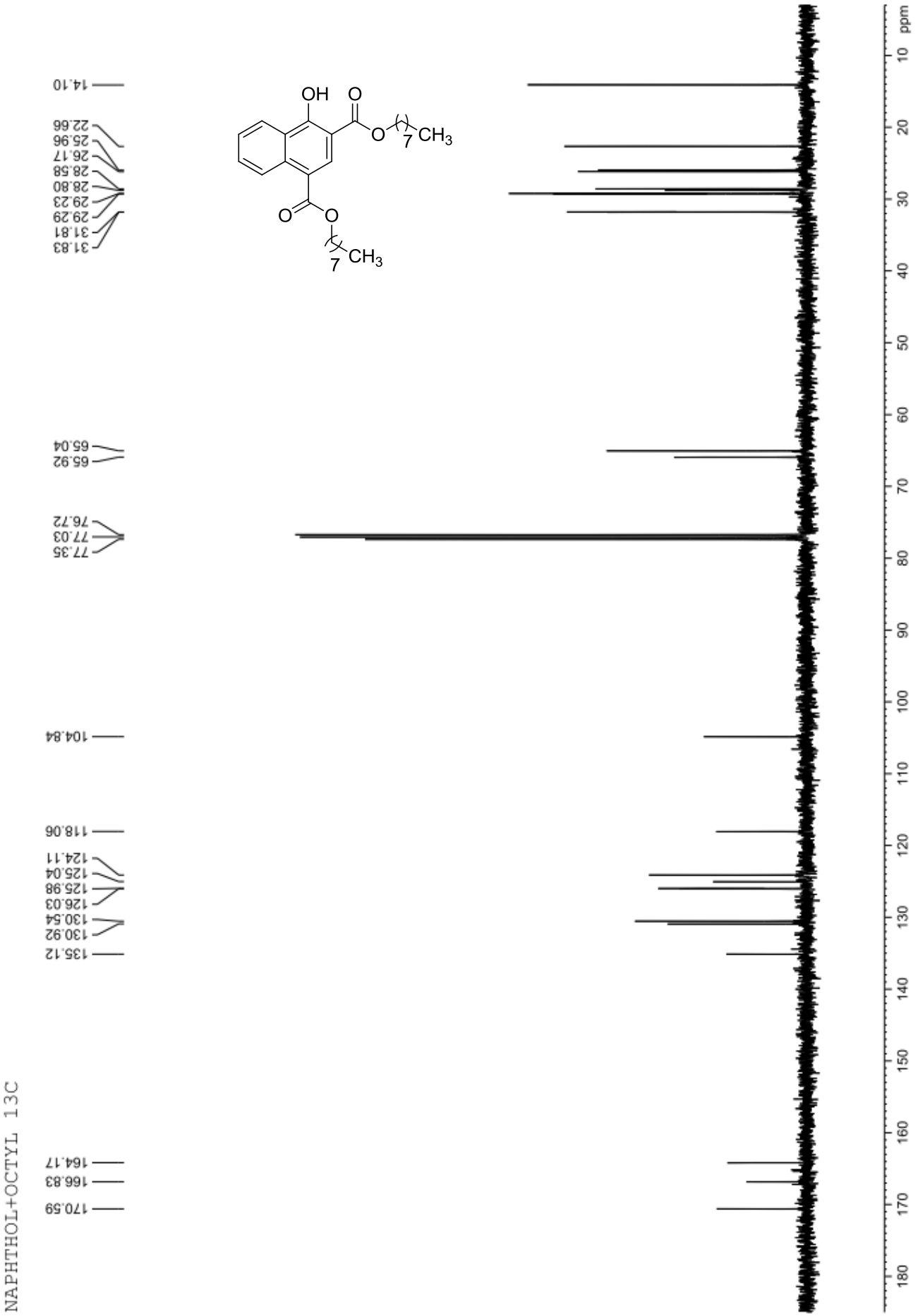

naphthol+amyl 13C
13.99
14.05
22.34
22.40
28.10
28.24
28.34
28.46
65.02
65.92
76.74
77.06
77.37
104.81
117.97
124.09
125.01
125.96
126.02
130.55
130.93
135.12
164.16
166.80
170.58
OH
O
O
4
CH3
O
O
4
CH3
ppm

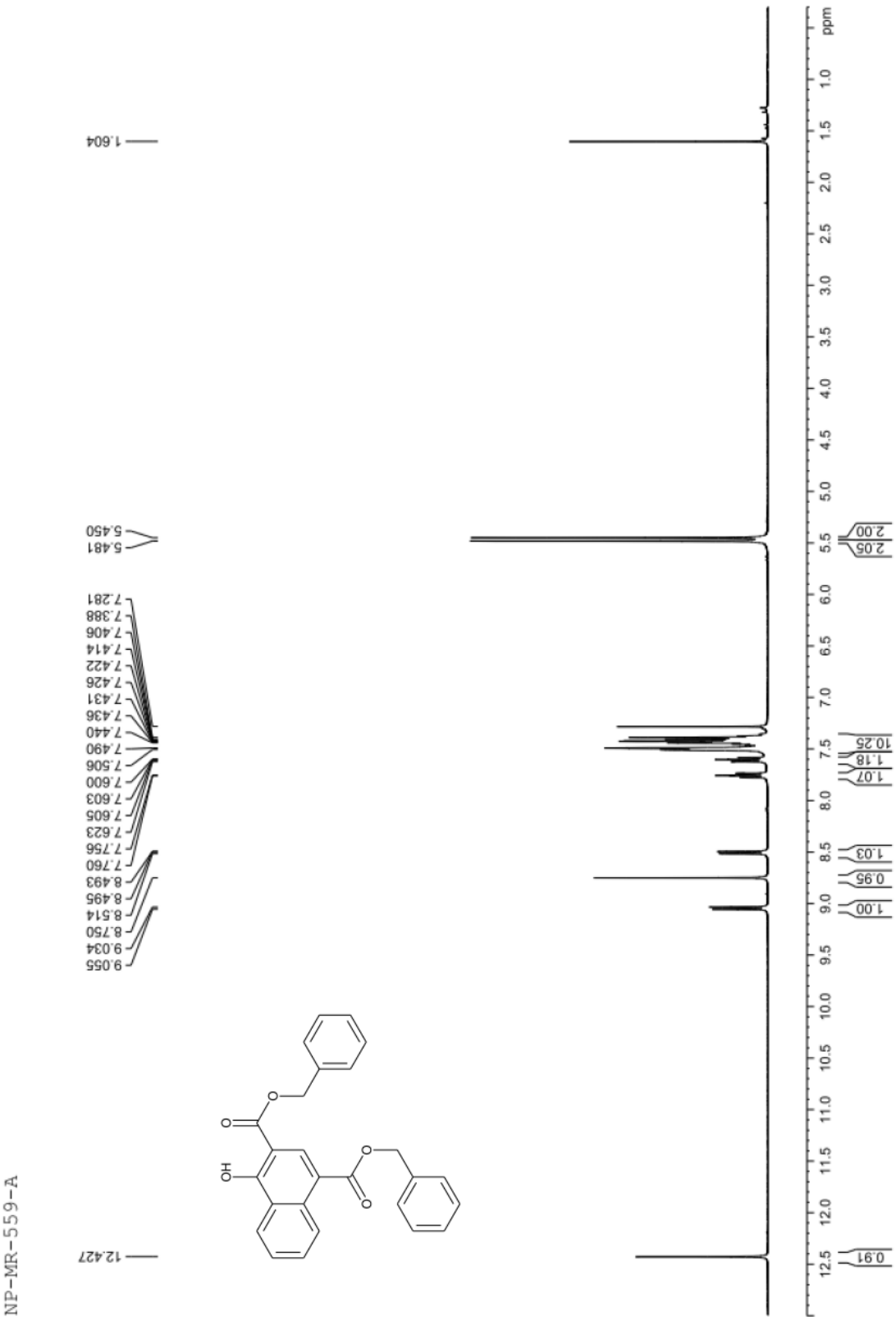
naphthol+hexnol 1H

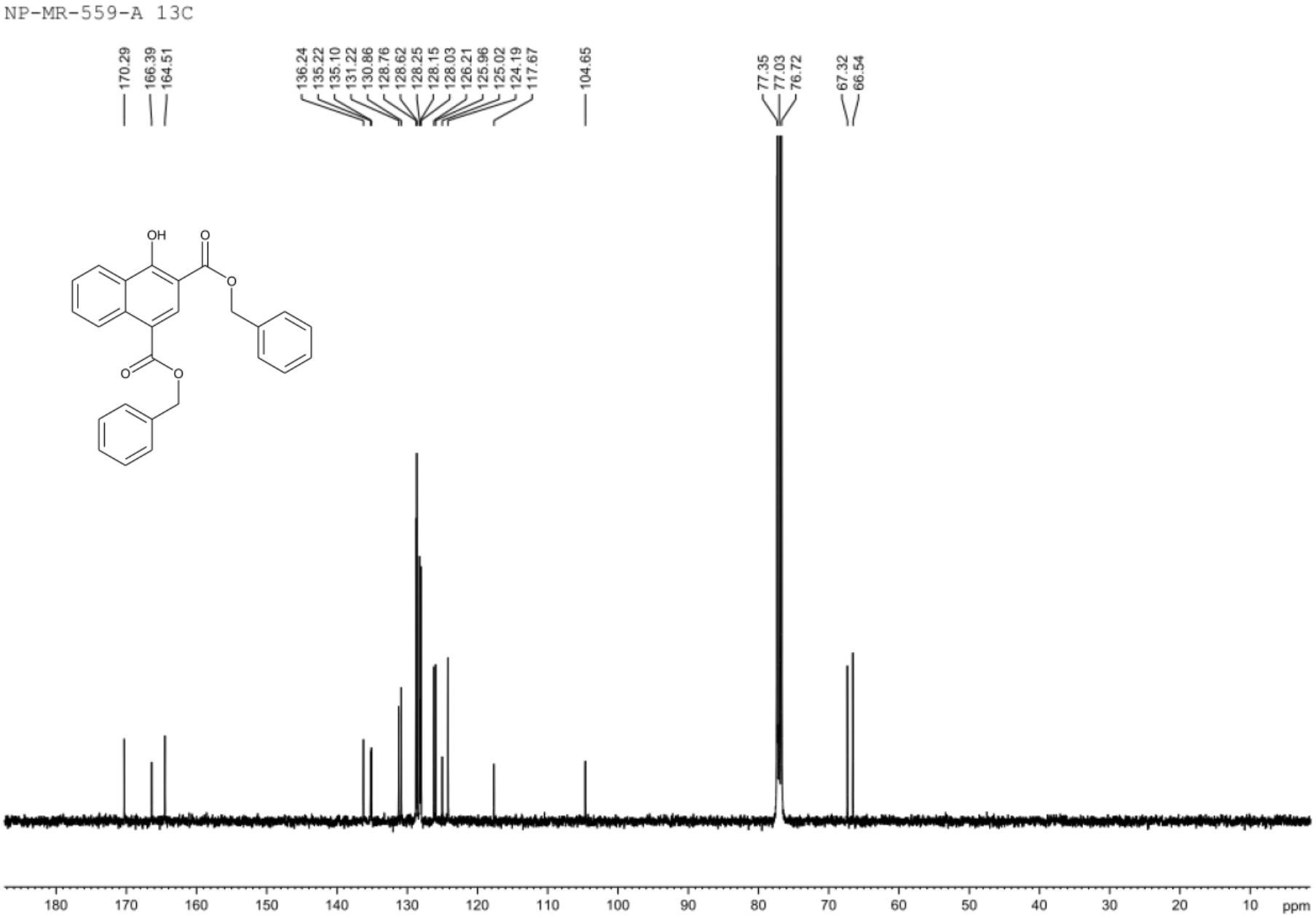



naphthol+hexyl 13C
14.02
22.55
22.60
25.61
25.82
28.52
28.74
31.42
31.49
65.04
65.93
76.71
77.03
77.35
104.84
118.04
124.11
125.04
125.97
126.03
130.52
130.93
135.13
164.18
166.83
170.61
OH
O
O
5
CH3
O
O
5
CH3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

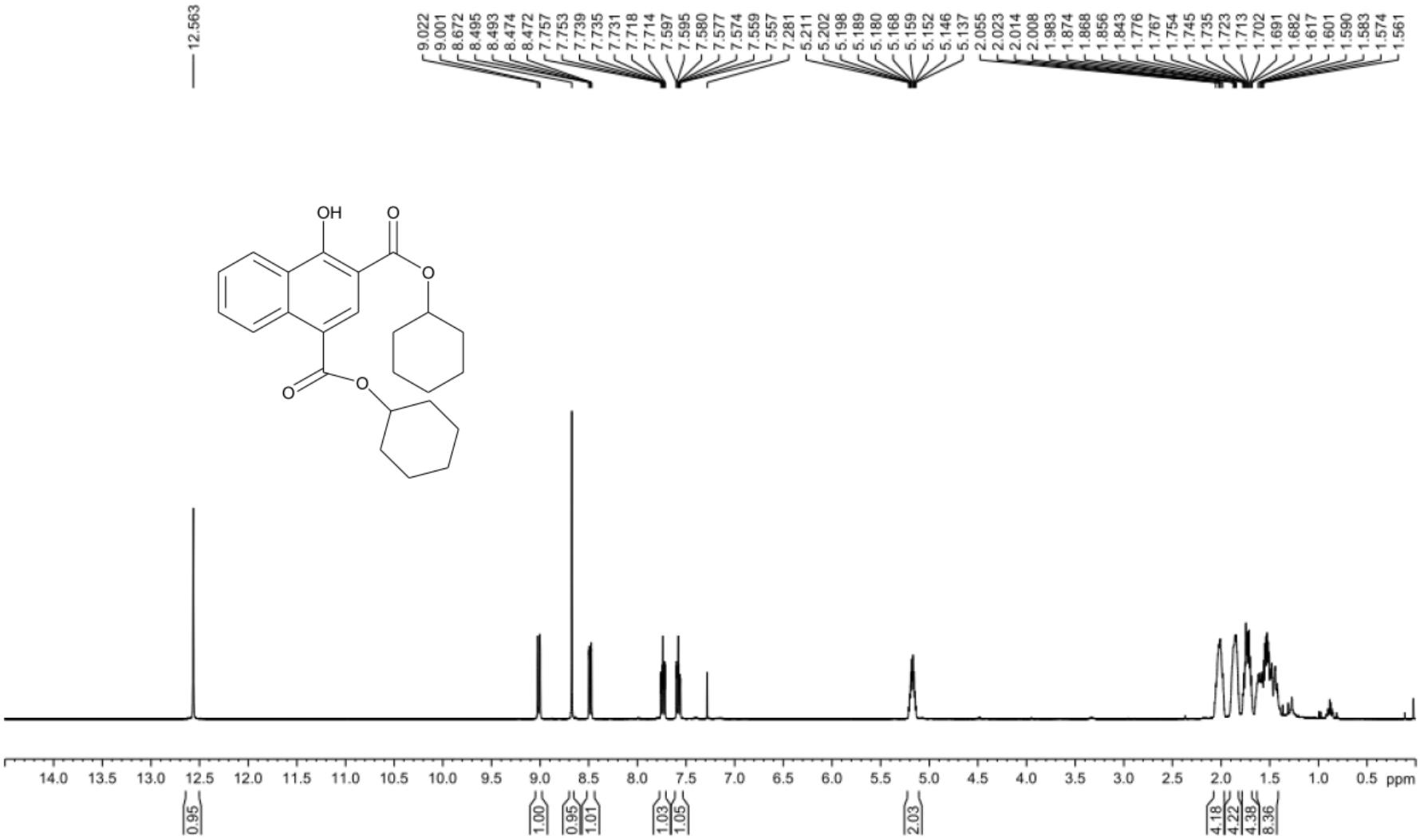

NAPHTHOL+OCTYL 1H
OH
O
O
7
CH3
O
O
7
CH3
ppm
6.28
16.07
4.17
4.18
4.00
1.08
1.08
1.05
0.96
0.99
1.01
12.498
9.033
9.011
8.638
8.505
8.484
7.766
7.763
7.749
7.745
7.742
7.727
7.724
7.607
7.588
7.569
7.281
4.456
4.439
4.423
4.406
4.389
1.886
1.879
1.869
1.862
1.852
1.842
1.832
1.826
1.815
1.537
1.518
1.504
1.483
1.467
1.424
1.408
1.405
1.388
1.372
1.359
1.344
1.322
1.276
0.926
0.913
0.909
0.895


NAPHTHOL+OCTYL 13C
14.10
22.66
25.96
26.17
28.58
28.80
29.23
29.29
31.81
31.83
65.04
65.92
76.72
77.03
77.35
104.84
118.06
124.11
125.04
125.98
126.03
130.54
130.92
135.12
164.17
166.83
170.59
OH
O
O
7
CH3
O
O
7
CH3
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
ppm

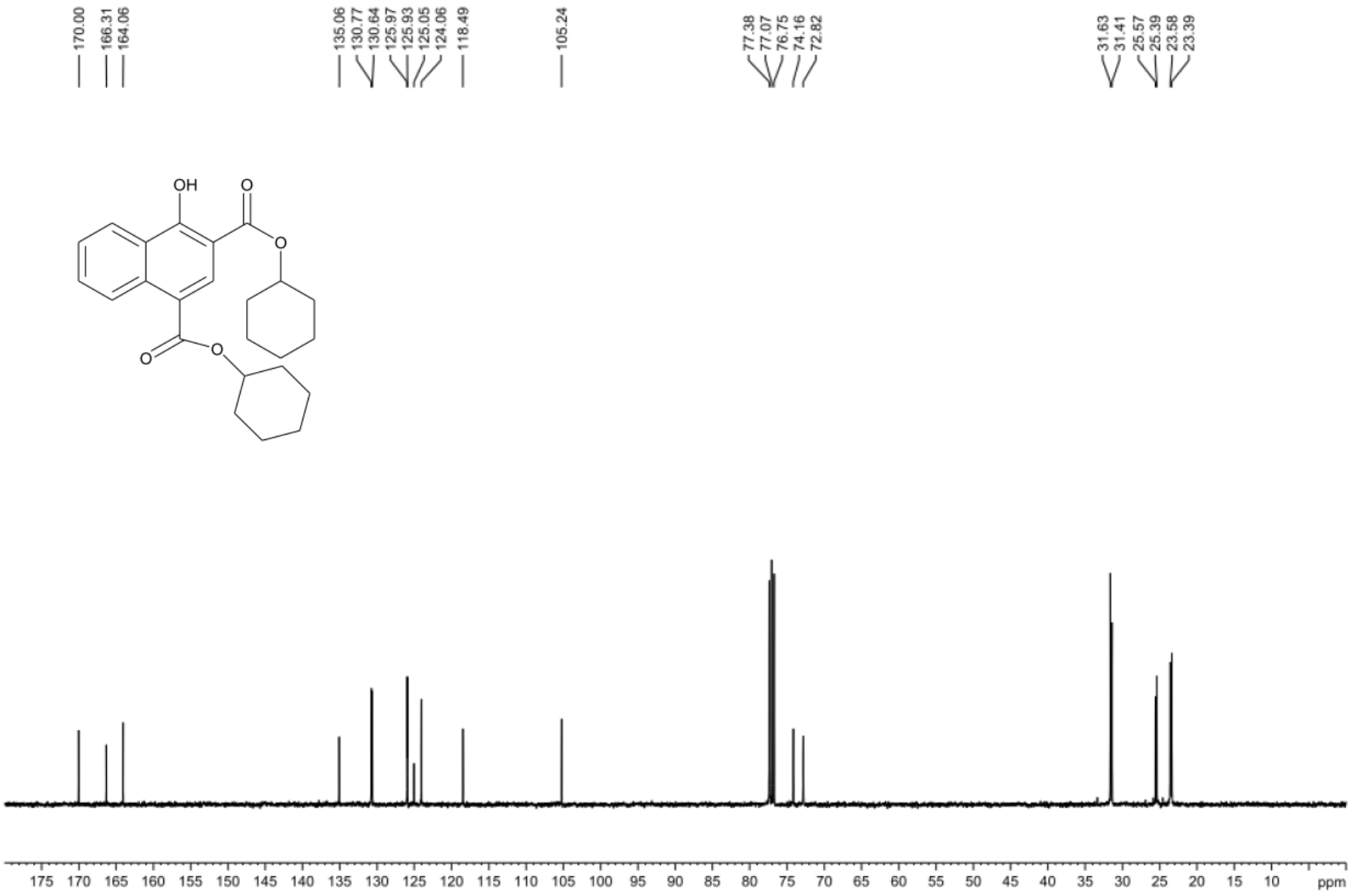

NP-MR-559-A
12.427
9.055
9.034
8.750
8.514
8.495
8.493
7.760
7.756
7.623
7.605
7.603
7.600
7.506
7.490
7.440
7.436
7.431
7.426
7.422
7.414
7.406
7.388
7.281
5.481
5.450
1.604
OH
O
O
O
O
ppm
0.91
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.00
0.95
1.03
1.07
1.18
10.25
2.05
2.00


NP-MR-559-A 13C
170.29
166.39
164.51
136.24
135.22
135.10
131.22
130.86
128.76
128.62
128.25
128.15
128.03
126.21
125.96
125.02
124.19
117.67
104.65
77.35
77.03
76.72
67.32
66.54
OH
O
O
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

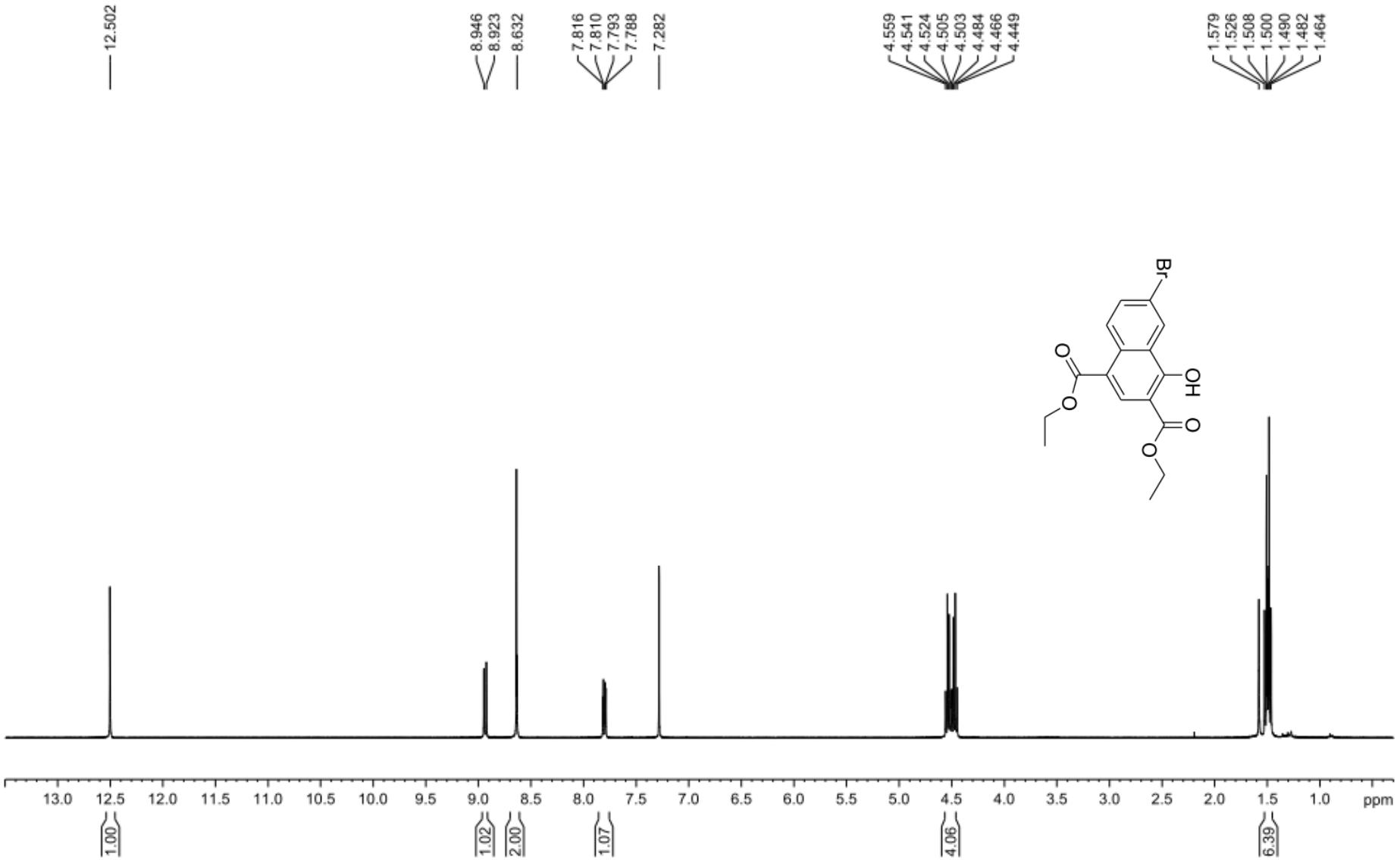
NP-cyclohexyl of naphthol

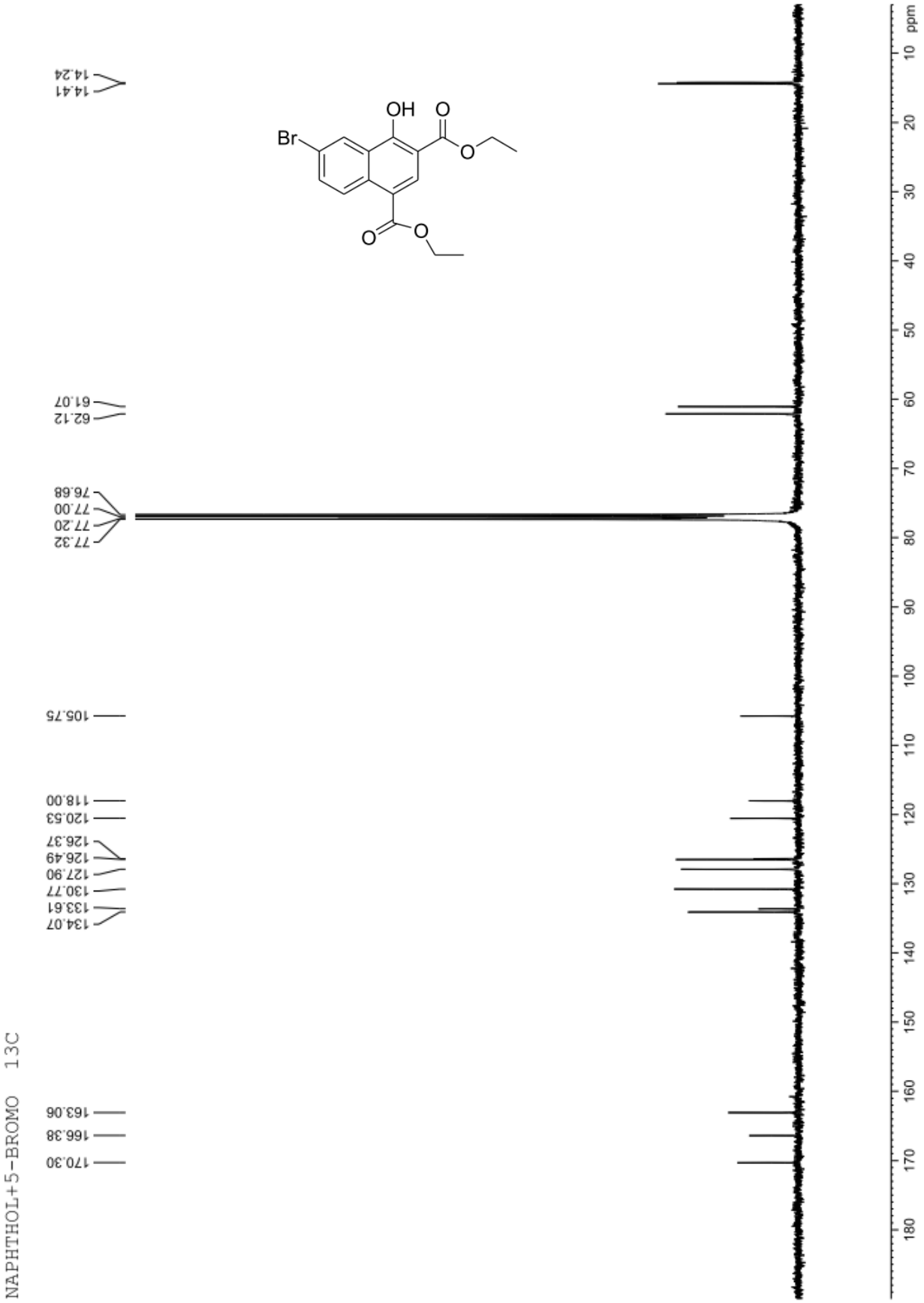


naphthol-cyclohexyl 13C

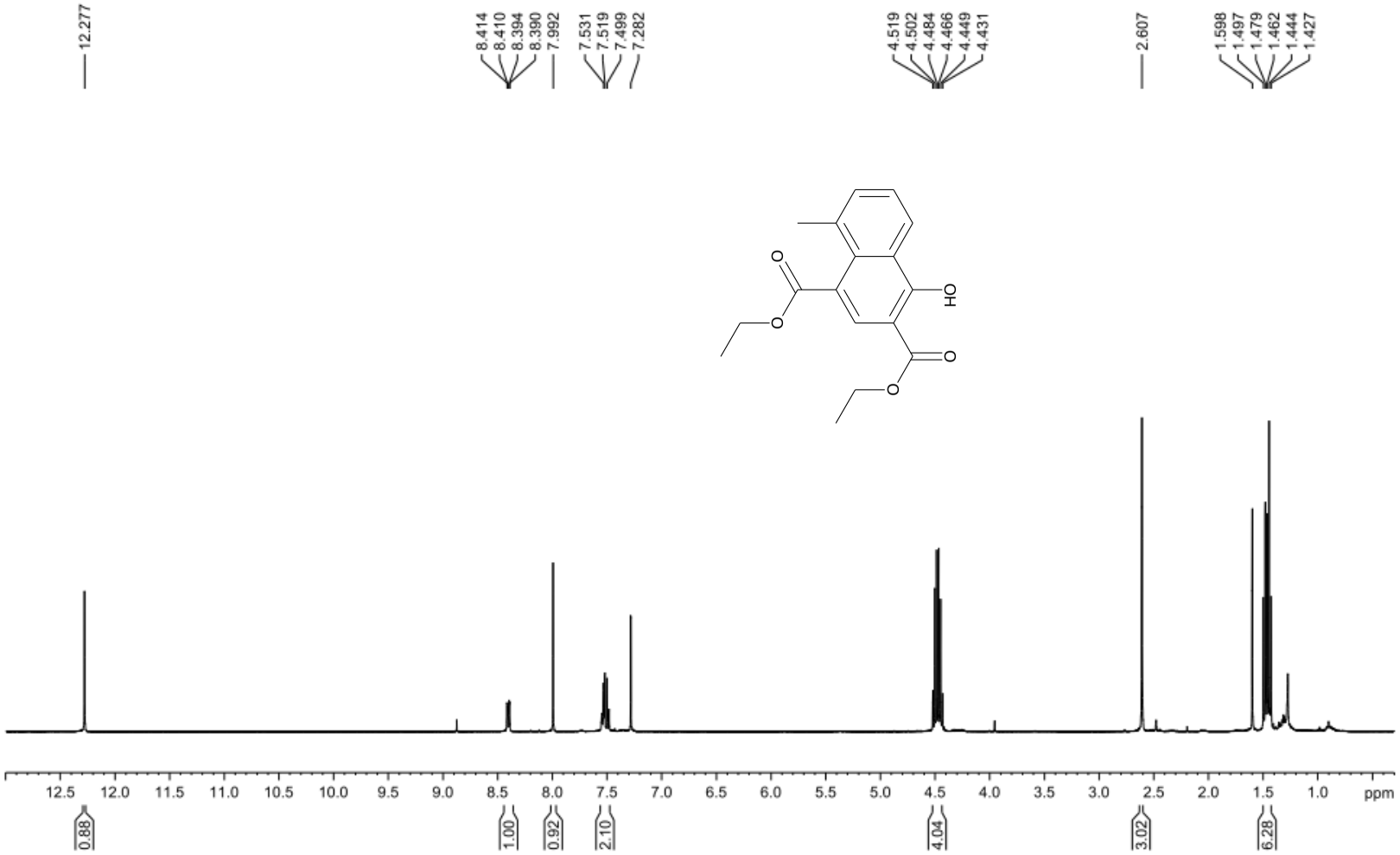


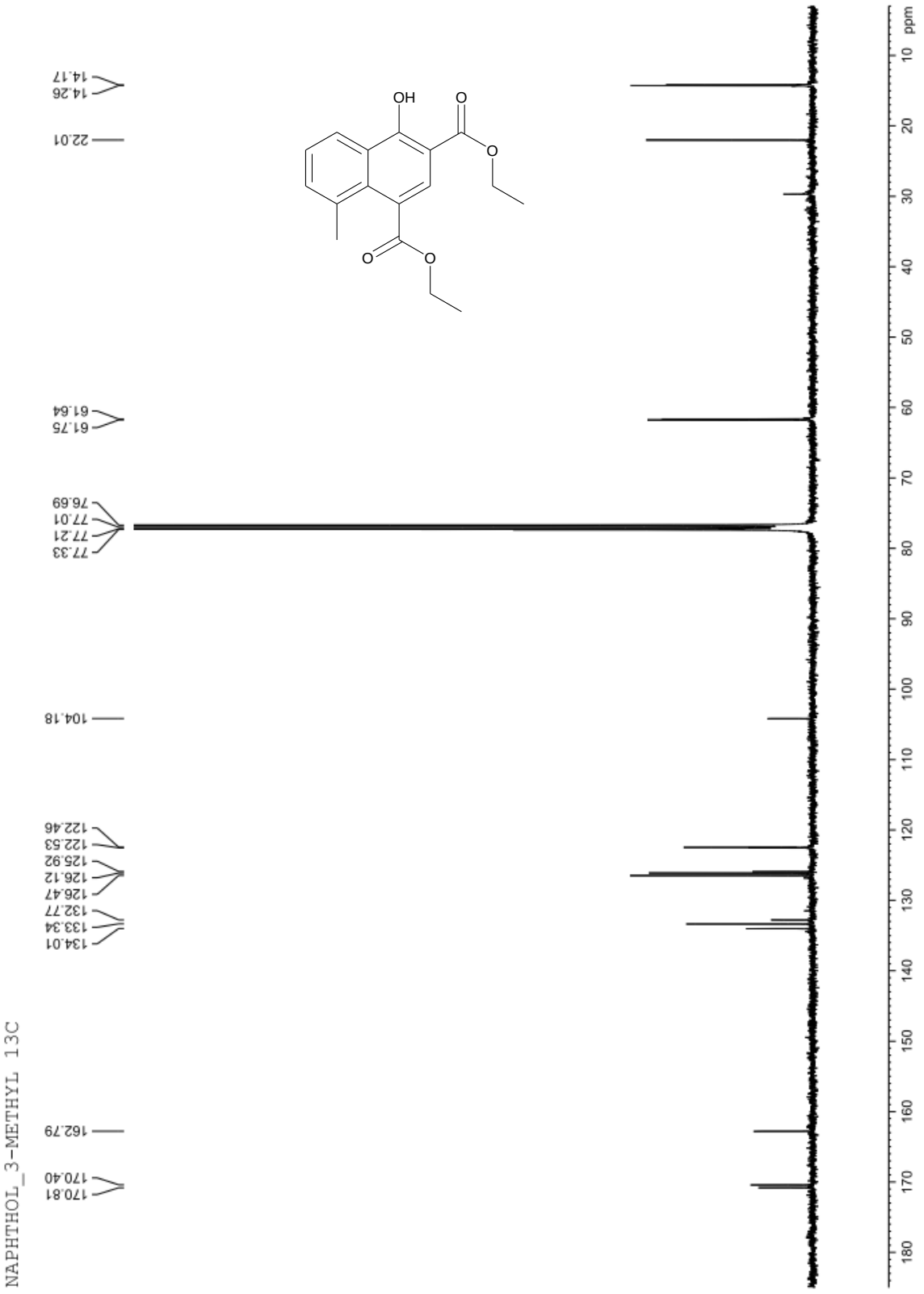
naphthol+5-BROMO 1H

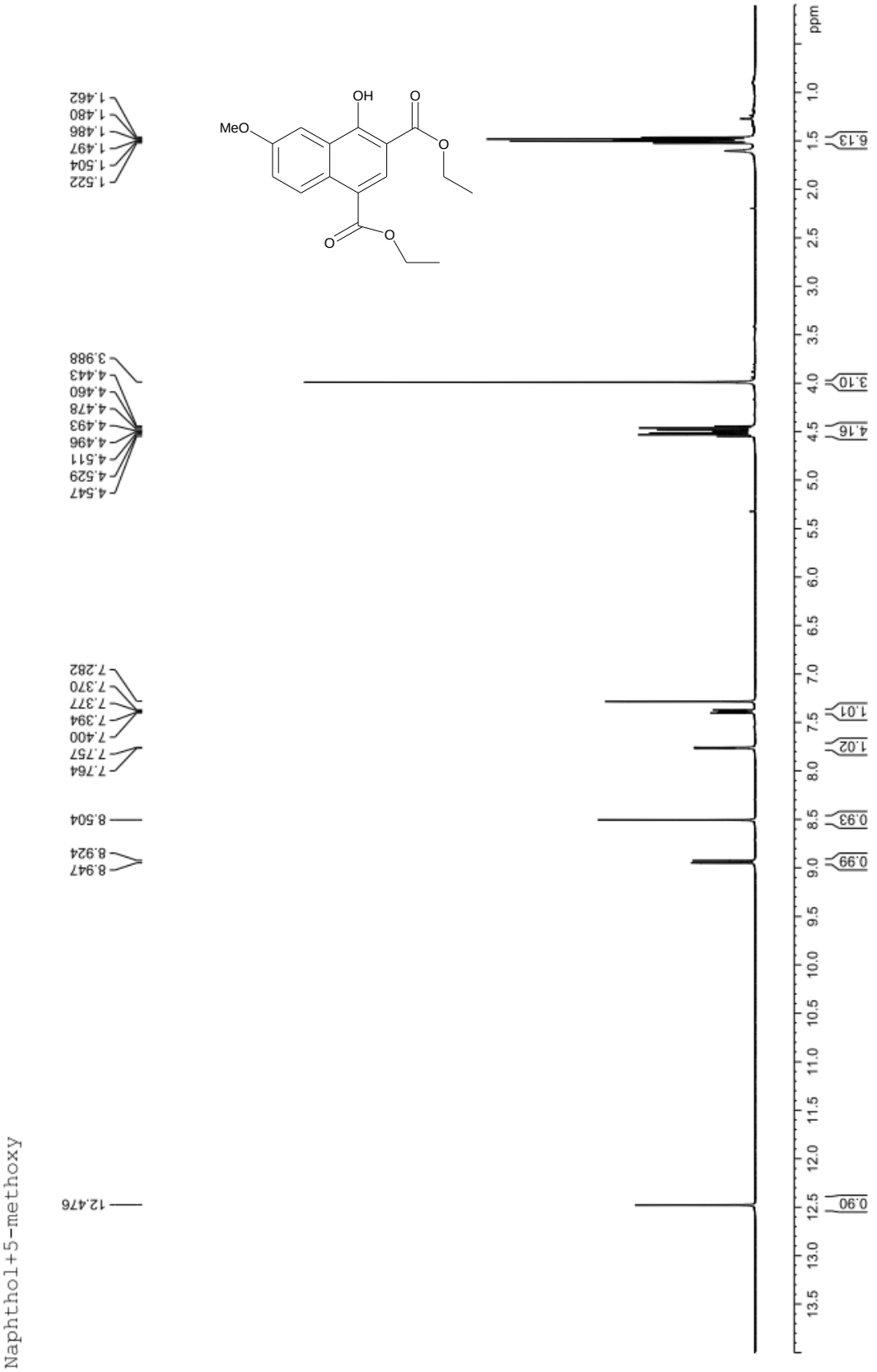


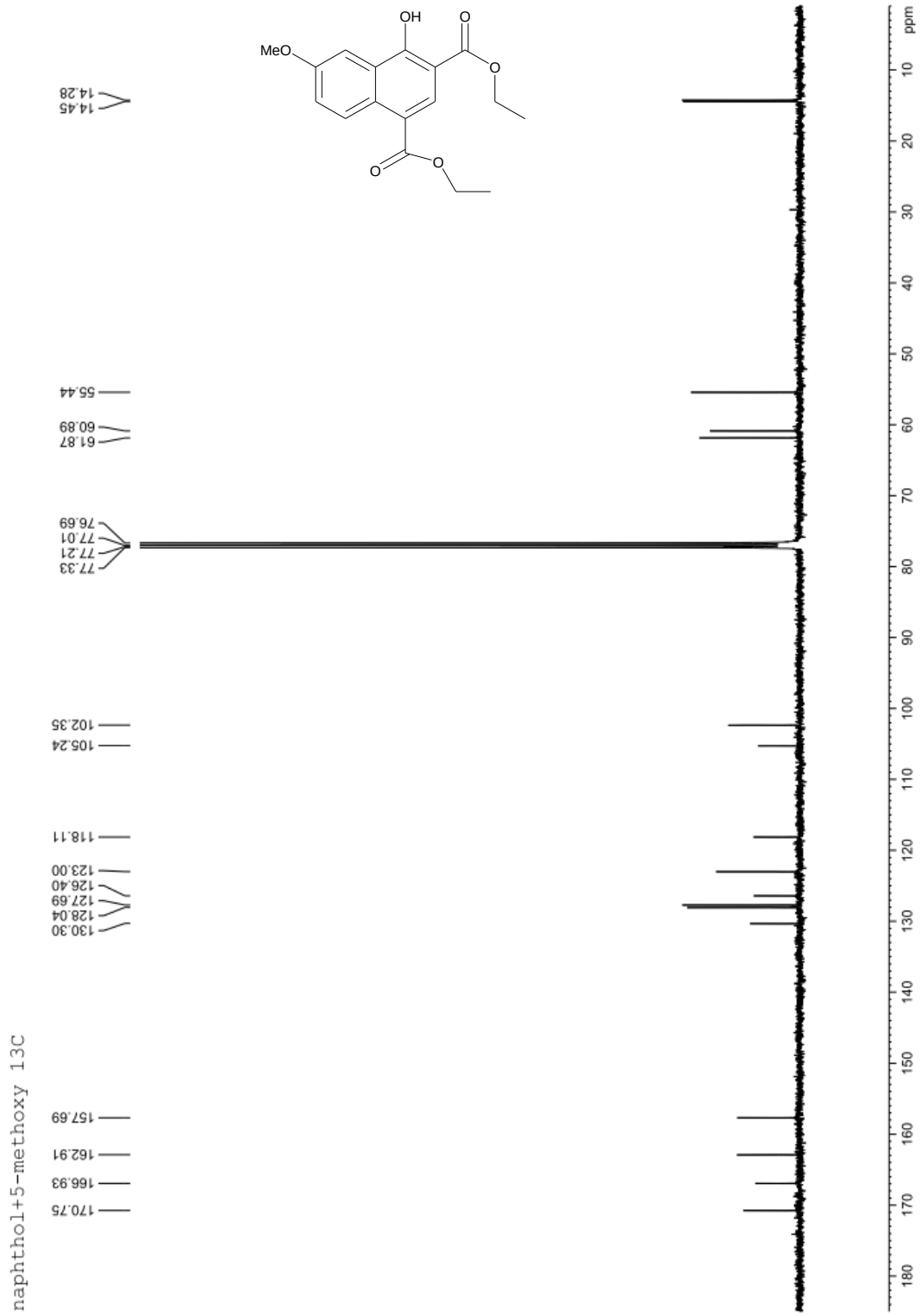

NAPHTHOL+5-BROMO 13C
14.24
14.41
61.07
62.12
76.68
77.00
77.20
77.32
105.75
118.00
120.53
126.37
126.49
127.90
130.77
133.61
134.07
163.06
166.38
170.30
OH
O
Br
O
O
O
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

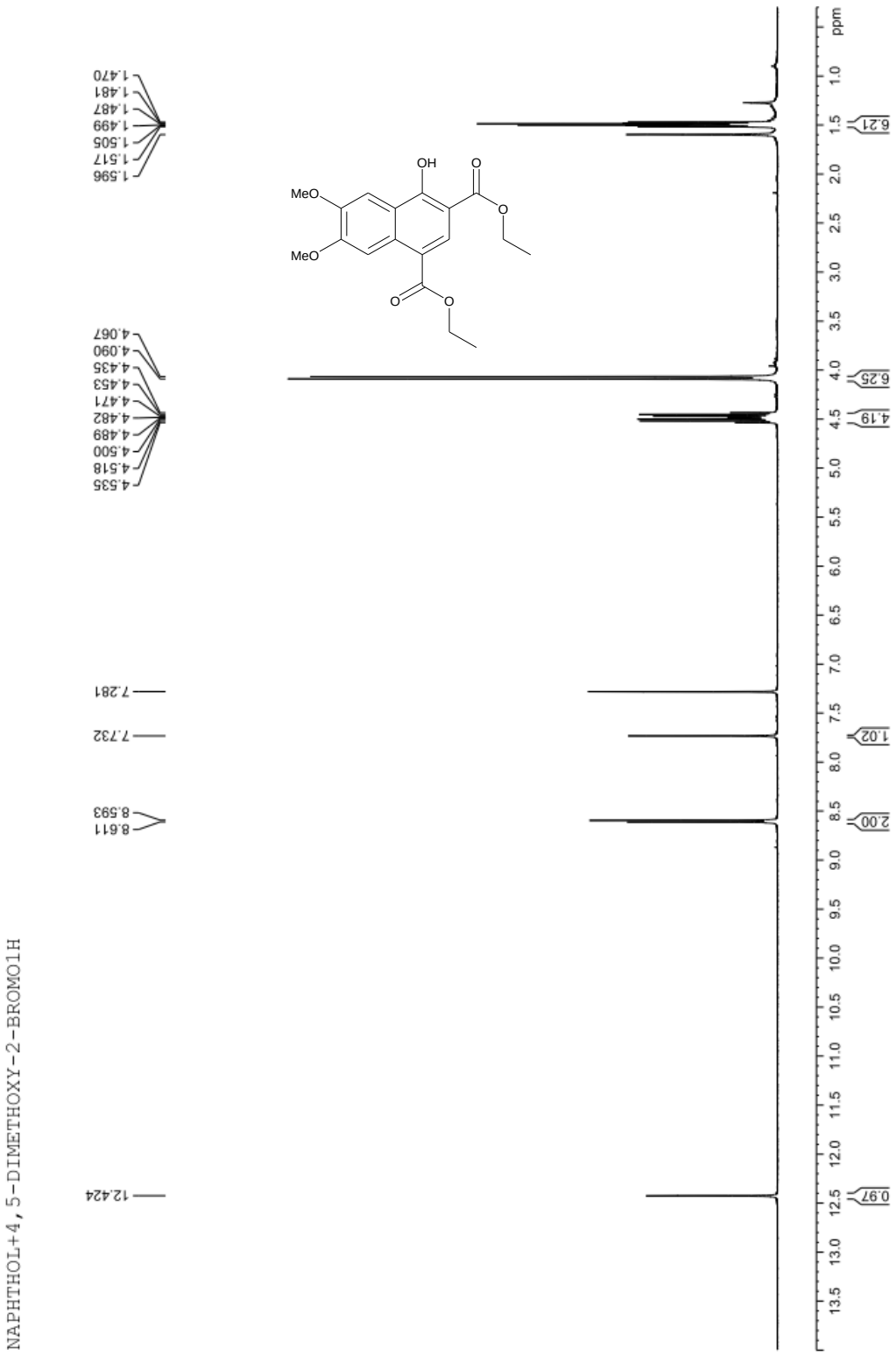
naphthol+3-methyl 1H

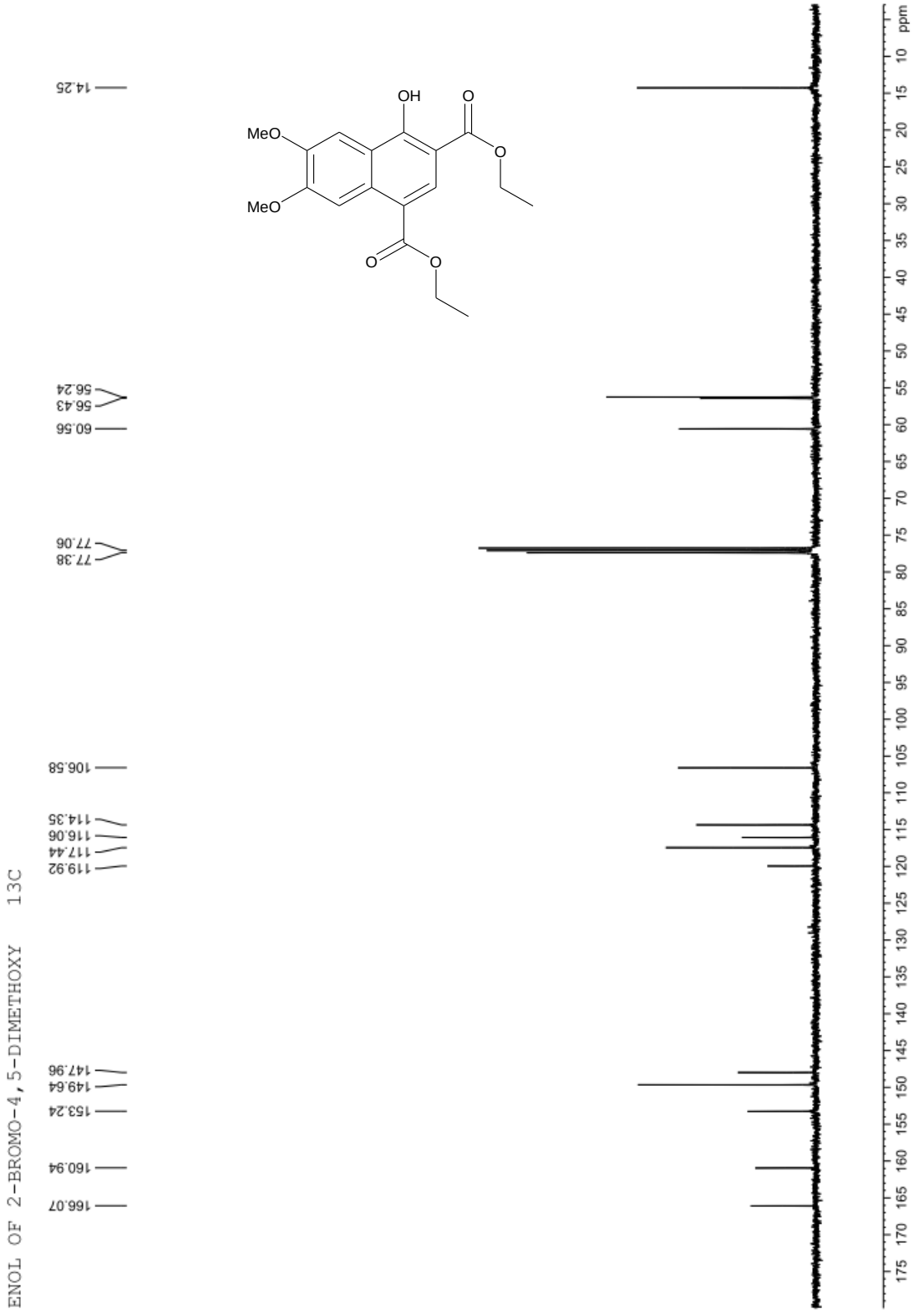



NAPHTHOL_3-METHYL 13C
14.17
14.26
22.01
61.64
61.75
76.69
77.01
77.21
77.33
104.18
122.46
122.53
125.92
126.12
126.47
132.77
133.34
134.01
162.79
170.40
170.81
OH
O
O
O
O
ppm

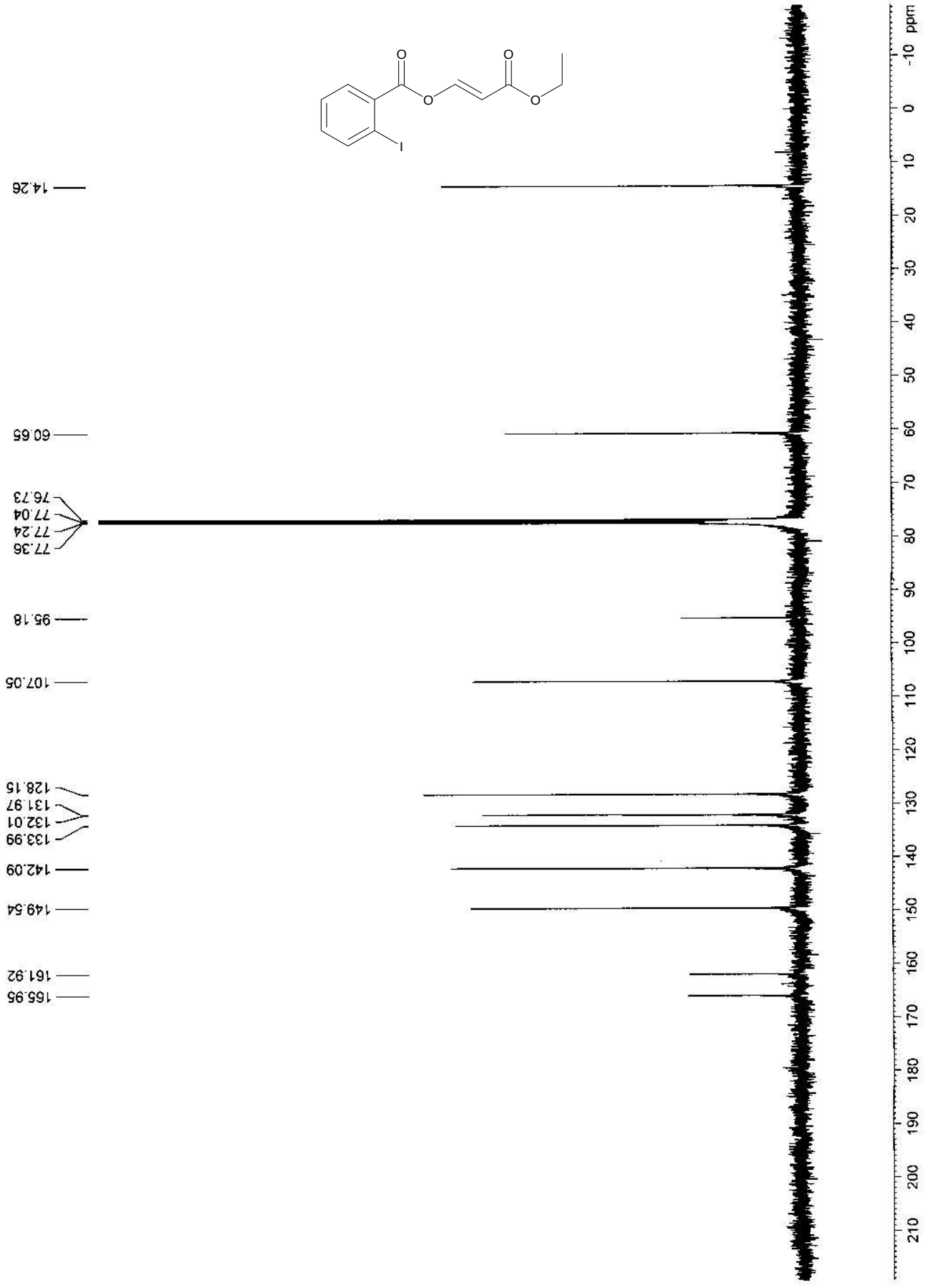

Naphthol+5-methoxy
12.476
8.947
8.924
8.504
7.764
7.757
7.400
7.394
7.377
7.370
7.282
4.547
4.529
4.511
4.496
4.493
4.478
4.460
4.443
3.988
1.522
1.504
1.497
1.486
1.480
1.462
MeO
OH
O
O
O
O
ppm
0.90
0.99
0.93
1.02
1.01
4.16
3.10
6.13


naphthol+5-methoxy 13C
170.75
166.93
162.91
157.69
130.30
128.04
127.69
126.40
123.00
118.11
105.24
102.35
77.33
77.21
77.01
76.69
61.87
60.89
55.44
14.45
14.28
OH
O
O
MeO
O
O
ppm


NAPHTHOL+4,5-DIMETHOXY-2-BROMO1H
12.424
8.611
8.593
7.732
7.281
4.535
4.518
4.500
4.489
4.482
4.471
4.453
4.435
4.090
4.067
1.596
1.517
1.505
1.499
1.487
1.481
1.470
OH
O
O
O
O
MeO
MeO
ppm
0.97
2.00
1.02
4.19
6.25
6.21


ENOL OF 2-BROMO-4,5-DIMETHOXY 13C
14.25
56.24
56.43
60.56
77.06
77.38
106.58
114.35
116.06
117.44
119.92
147.96
149.64
153.24
160.94
166.07
OH
O
O
MeO
MeO
O
O
ppm

1.359
1.341
1.323
4.294
4.276
4.258
4.240
5.942
5.911
7.245
7.260
7.264
7.282
7.473
7.475
7.492
7.511
7.514
7.965
7.969
7.984
7.988
8.085
8.087
8.105
8.107
8.523
8.554
O
O
O
O
I
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
3.40
2.16
1.00
1.40
1.02
1.03
0.97
1.00


O
O
O
O
I
14.26
60.65
76.73
77.04
77.24
77.36
95.18
107.05
128.15
131.97
132.01
133.99
142.09
149.54
161.92
165.95
ppm
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

Future Work

Future prospect of Part I

In line with our work on stereoselective enamide synthesis, it may be envisioned Pd-based catalysts may promote the addition of N−H nucleophiles (from thioamides and sulphonamides) to the carbon-carbon multiple bond to form corresponding enamide derivatives. Moreover, such efforts are less literature precedent and are the future work in this field. Additionally, development of suitable reaction conditions for the addition of amides, thioamidesand sulphonamides to electronically rich olefins or alkynes is considered as a future objective.

Future prospect of Part II

In Part II, we have synthesized enol esters from the reaction of acid and electron deficient alkynes in the presence of base. However, our method is ineffective when electronically rich alkyne was used. Synthesis of such enol ester is a current challenge and can be addressed in future. Furthermore, we have demonstrated an unprecedented application of enol esters in naphthol synthesis. At that time, our effort towards the synthesis of isocoumarin derivatives was unsuccessful. Efficacious synthesis of isocoumarin derivatives by intramolecular cyclization of such enol esters has been considered as the future scope of this work.

List of Publications

1. N. Panda,* A. K. Jena,[†]**M. Raghavender**,[†] "Stereoselective Synthesis of Enamides by Palladium Catalyzed Coupling of Amides with Electron Deficient Olefins" *ACS catalysis*, **2012**, *2*, 539-545. ([†]Contributed equally)
2. N. Panda,* and **R. Mothkuri**, "Stereoselective Synthesis of Enamides by Palladium-Catalyzed Hydroamidation of Electron Deficient Terminal Alkynes" *Journal of Organic Chemistry*, **2012**, *77*, 9407-9412.
3. N. Panda,***R. Mothkuri**, A. Pal, A.R. Paital "Copper-catalyzed Synthesis of α-Naphthols from Enol Esters"*Advanced Synthesis & Catalysis*, **2013**, *355*, 2809-2814.
4. N. Panda,* **R. Mothkuri** and D. K. Nayak "Copper-Catalyzed Regioselective Synthesis of *N*-aryl Amides from Aldoximes and Aryl Halides" *European Journal of Organic Chemistry*, **2014**, 1602
5. N. Panda,* and **R. Mothkuri,** Synthesis of Substituted Oxazoles from Enamides" *New Journal of Chem*istry, **2014**, *38*, 5727-5735.